Financial Disclosures:

Richard P. Wenzel, MD, MSc

Virginia Commonwealth University

Period 2008-2011

Advisory Boards

Rib-x Boehringer-Ingelheim

Pfizer BioMerieux

Xoma Sanofi-Aventis

BD Diagnostics

Research Study support

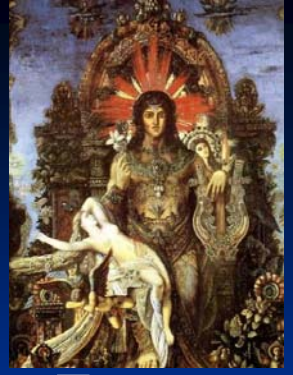
Vestagen

Honorarium-Travel Funds

3M

Co-evolution of Infection Control and Antibiotic Resistant Pathogens: What Works?

Richard P. Wenzel, M.D., M.Sc.
Professor and Former Chairman
Department of Internal Medicine
Medical College of Virginia
Virginia Commonwealth University



Legendary Inheritance of Sex, Violence and Tragedy Surrounding Staphylus

Zeus

Supreme ruler
Mt. Olympus
Married to Hera
Numerous liaisons
Father to Helen

Semele

Mortal priestess
Asked Zeus to reveal his glory -
Bolts of lightning led to death

Minos

King of Crete

Pasiphaë

Dionysus

God of wine
Hera had Titan lure and attack him
remaining heart back into Semele. "Twice born"

Ariadne

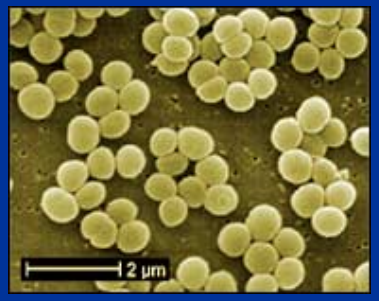
Loved Theseus who "had no joy for her" on Naxos

Staphylus

God of wine
Traveled with Jason for Golden Fleece

Staphylococcus Aureus

Dionysus

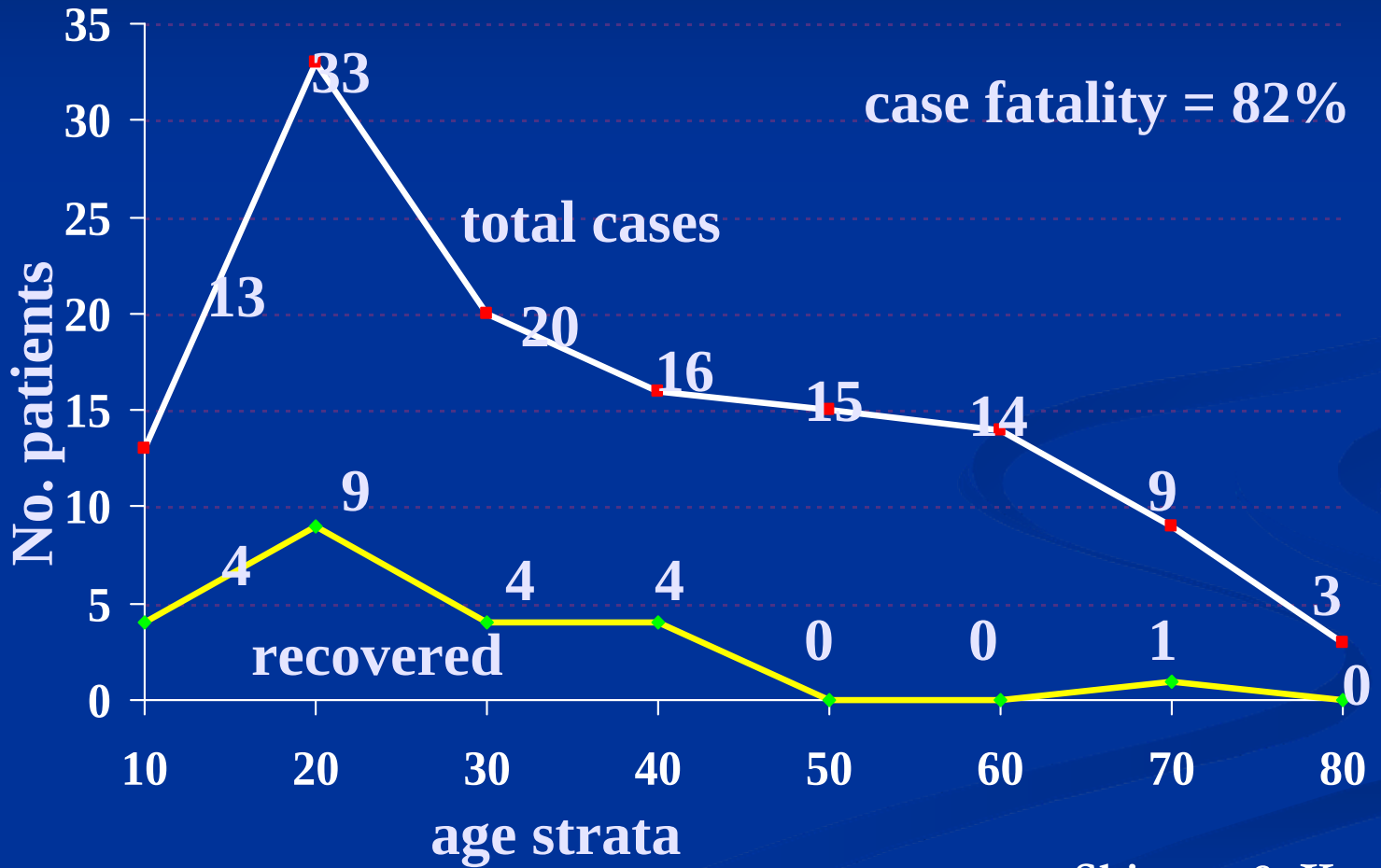


Sir Alexander Ogston

100 abscesses
Some in chains
Some in indigo-colored clumps
Reproduce abscess in mice by injection
Aureus: Latin – "gold"

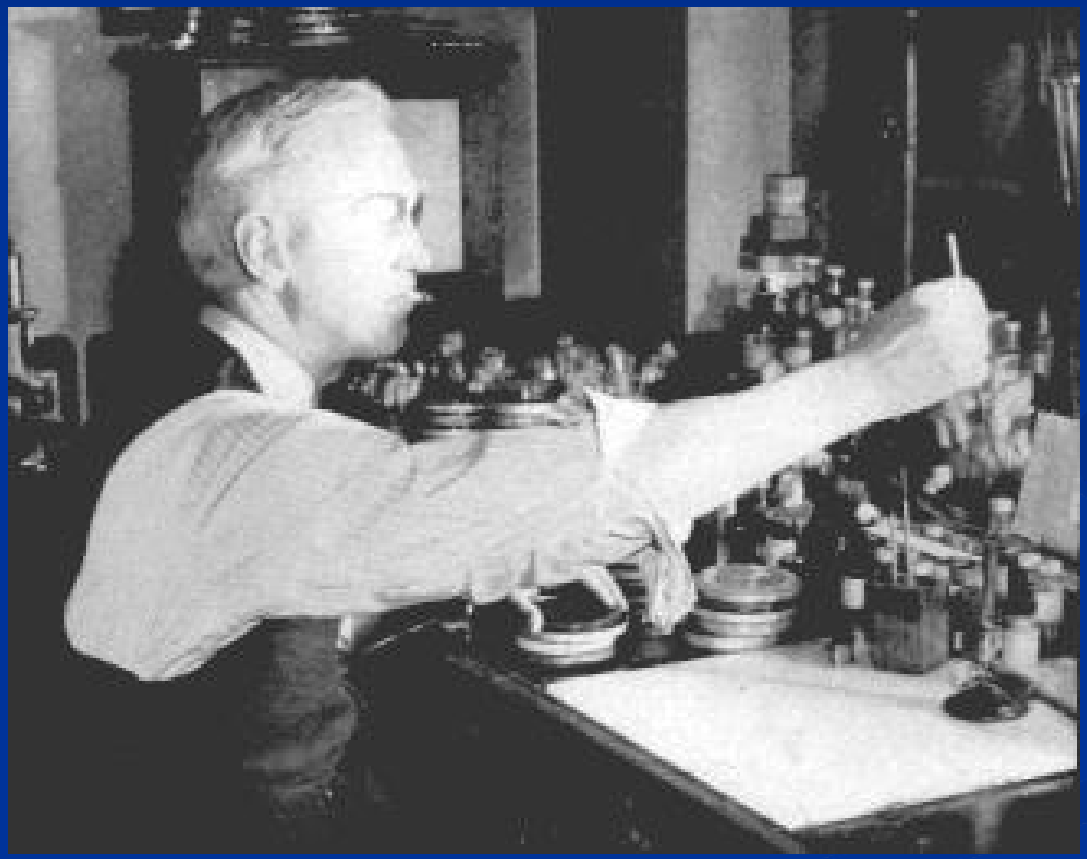
Scot Med J 1998; 43:156-7
Arch Klin Chir 1880; 25:588-

Significance of Bacteremia Caused by *Staphylococcus Aureus* (n=122)



Skinner & Keefer
Arch Int. Med 1941; 68: 851-75

Antibiotic Resistance in *S. aureus* Following the Great Discovery of Penicillin



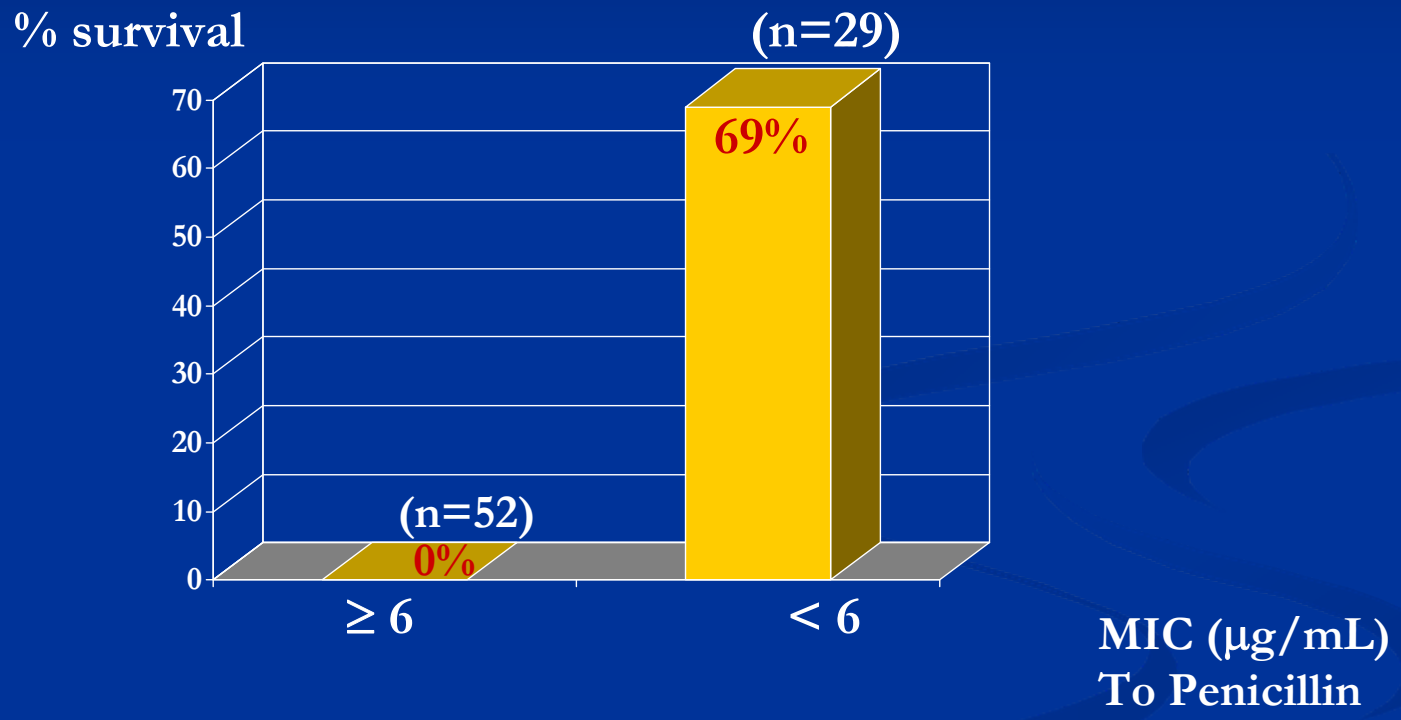
Sir Alexander Fleming

"An enzyme from bacteria Able to destroy Penicillin"

Extract of *E. coli* with a "substance destroying property of penicillin" – penicillinase

Abraham and Chain
Nature 1940; 146:837-

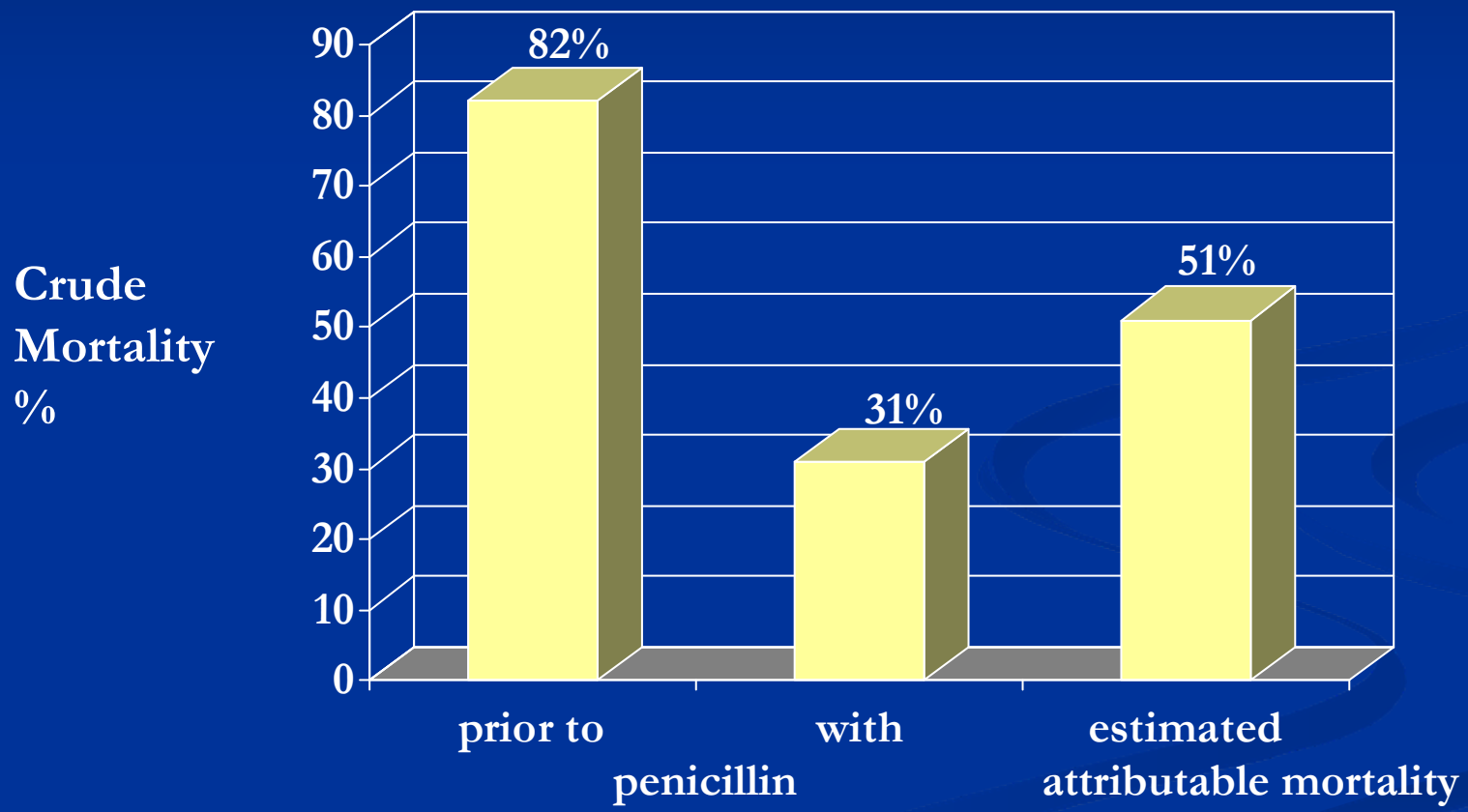
S. Aureus Bacteremia and Effective Antibiotic Rx



Abboud and Waisbren *Arch Intern Med* 1959; 104:226-33

Attributable Impact of Penicillin Estimated

- absolute 50% attributable survival -



Arch Int Med 1941; 68:851-75
Arch Int Med 1959; 104:226-73

Staphylococcal Toxin*
by P.N. Panton and F.C. O. Valentine

Denys and Van de Velde in 1895 described destruction of WBC after *S. aureus* injected into pleural cavities of rabbits: subsequent anti-leukocidin antibody

7/22 strains: strong leukoidin, weak hemolysis

6/7 severe infections, all 4 "pyemic" cases and

2/4 rapidly fatal after carbuncle

9/22 strains: weak leukocidin, strong hemolysis:

saprophytes

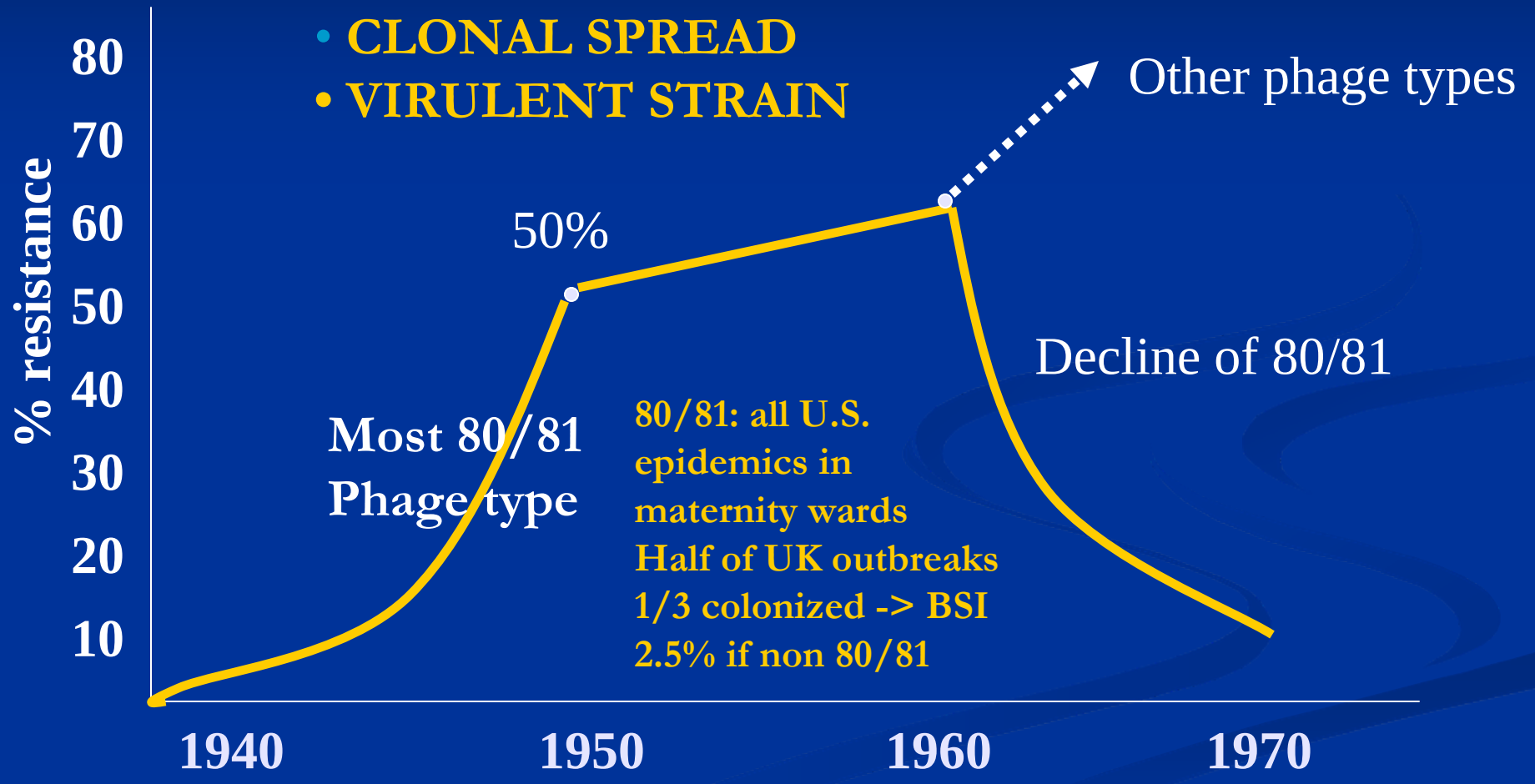
Antisera continuing anti-leukocidin antibodies

"chiefly efficacious with pyemic cases" in man

Lancet 1932 (March 5): 5068

* Gene later found to be on a phage virus integrated to Staph

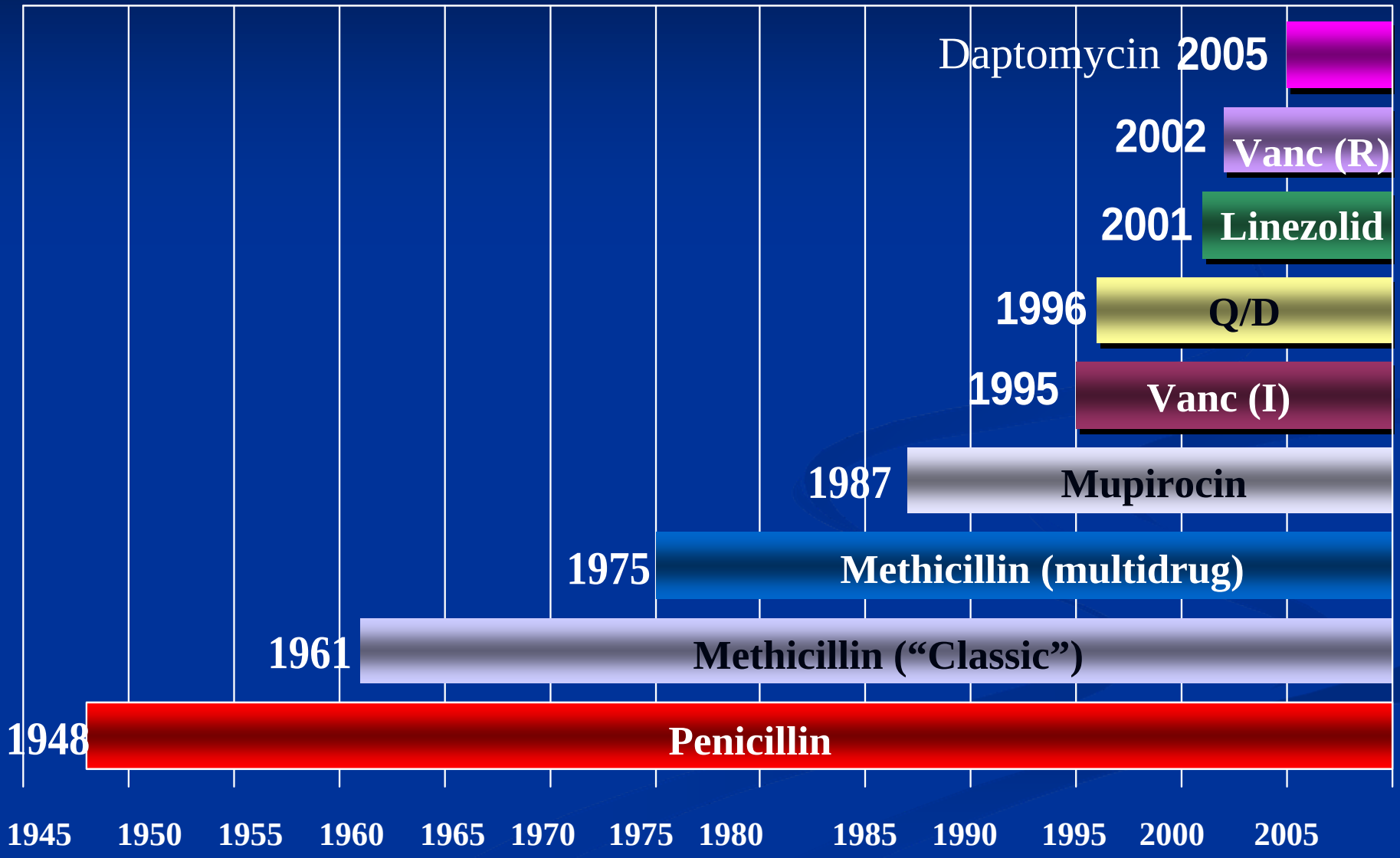
Penicillin-Resistant *S. aureus*: Lessons after 30 years 1940-70



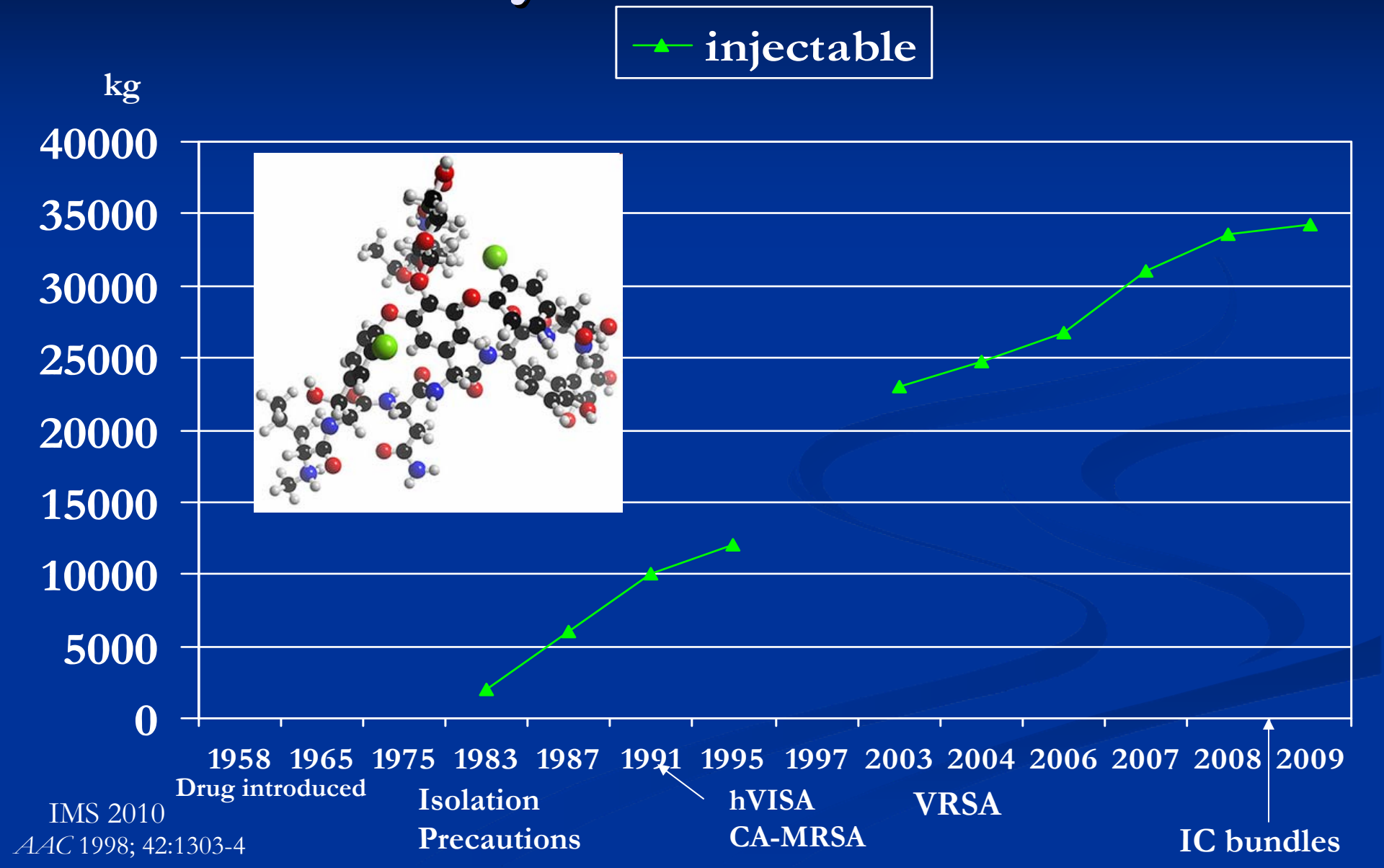
Lancet 1959; 1:190-5
BMJ 1959; 5153:658-62

Sci Based Med Ann Rev 1966; 157:73
Lancet 2005; 365:1256-8

S. aureus Resistance Timeline



Vancomycin Use in the US



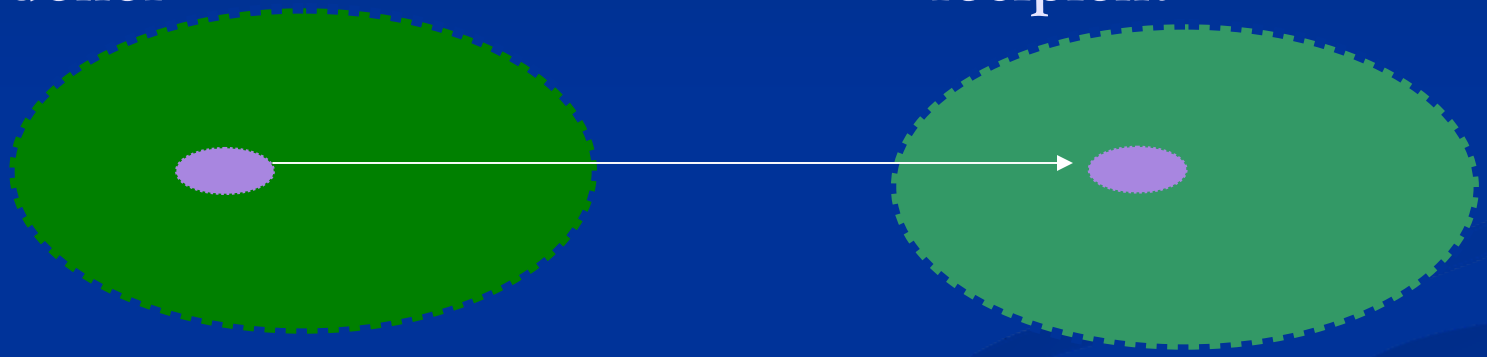
IMS 2010

AAC 1998; 42:1303-4

Enterococci Contain Sex-Pheromone Induced Plasmid Transfer

Plasmid containing donor

Plasmid free recipient

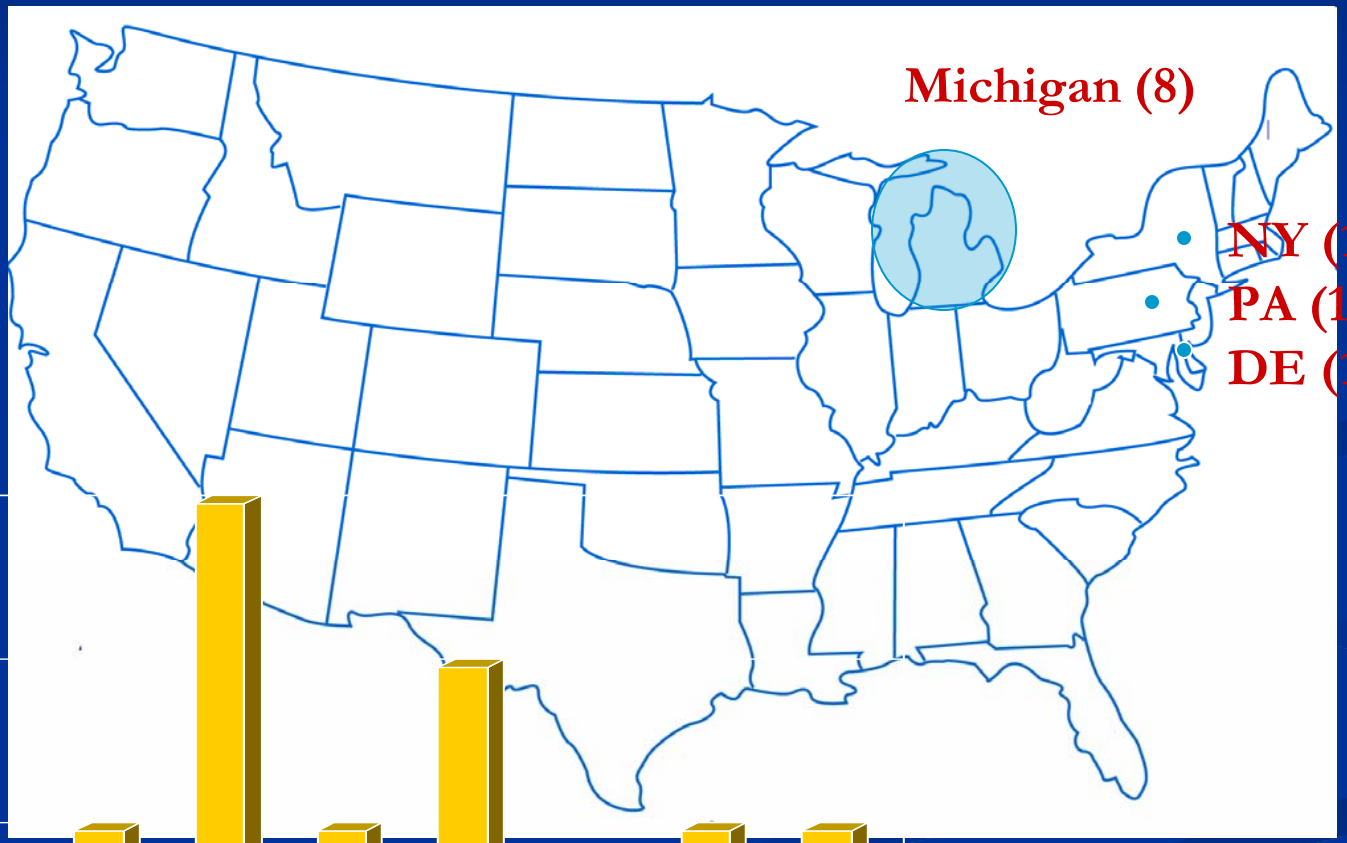


consenting (responsive)
- synthesize protein adhesin facilitating mating

Clewell
Cell 1993; 77: 9-12

secrete family of heat-stable protease (S)
pheromones (5 to 6) - 7 or 8 AA
result - - transfer
frequently 10^5 - 10^6 fold
after transfer - specific plasmid pheromone shut down

Eleven Cases of VRSA



Time Line for VRSA

CDCinfo@idsociety.org 5/6/10

Fully Vancomycin-Resistant *S. aureus* (n=11) 2002-2010

All prior: Vanco Rx, MRSA, VRE

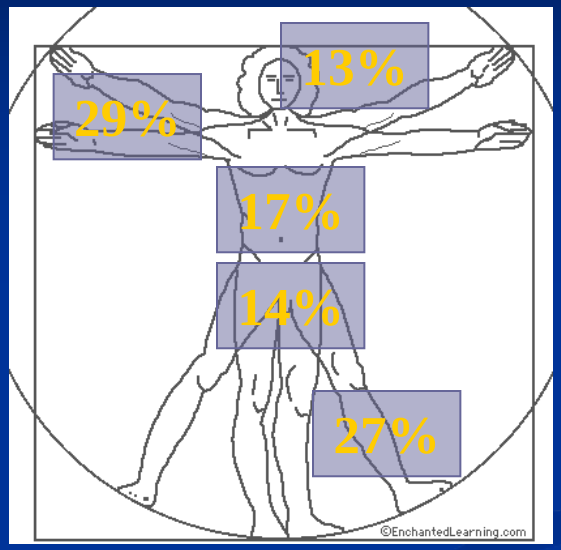
Condition	No	Age	No
D.M.	8	40s-50s	7
Obesity	4	60s-70s	4
ESRD	3		
Any above	10		
Wound	10		
Distal	7		
Extremity			

PHENOTYPE:

- Middle-aged adult
- Insulin resistance
- Distal extremity wound

CDC. IDSA Info@society.org 5/6/10

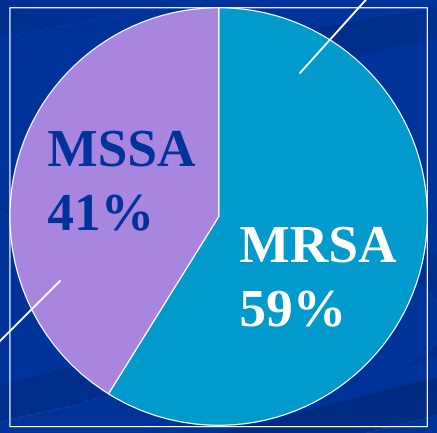
MRSA Infections in 422 ED Patients - 2004



***S.aureus* - 76% SSTI (MRSA 59%)**

Moran et al *NEJM* 2006; 355:666-74

USA 300 – 97%
SCC IV, PVL – 98%

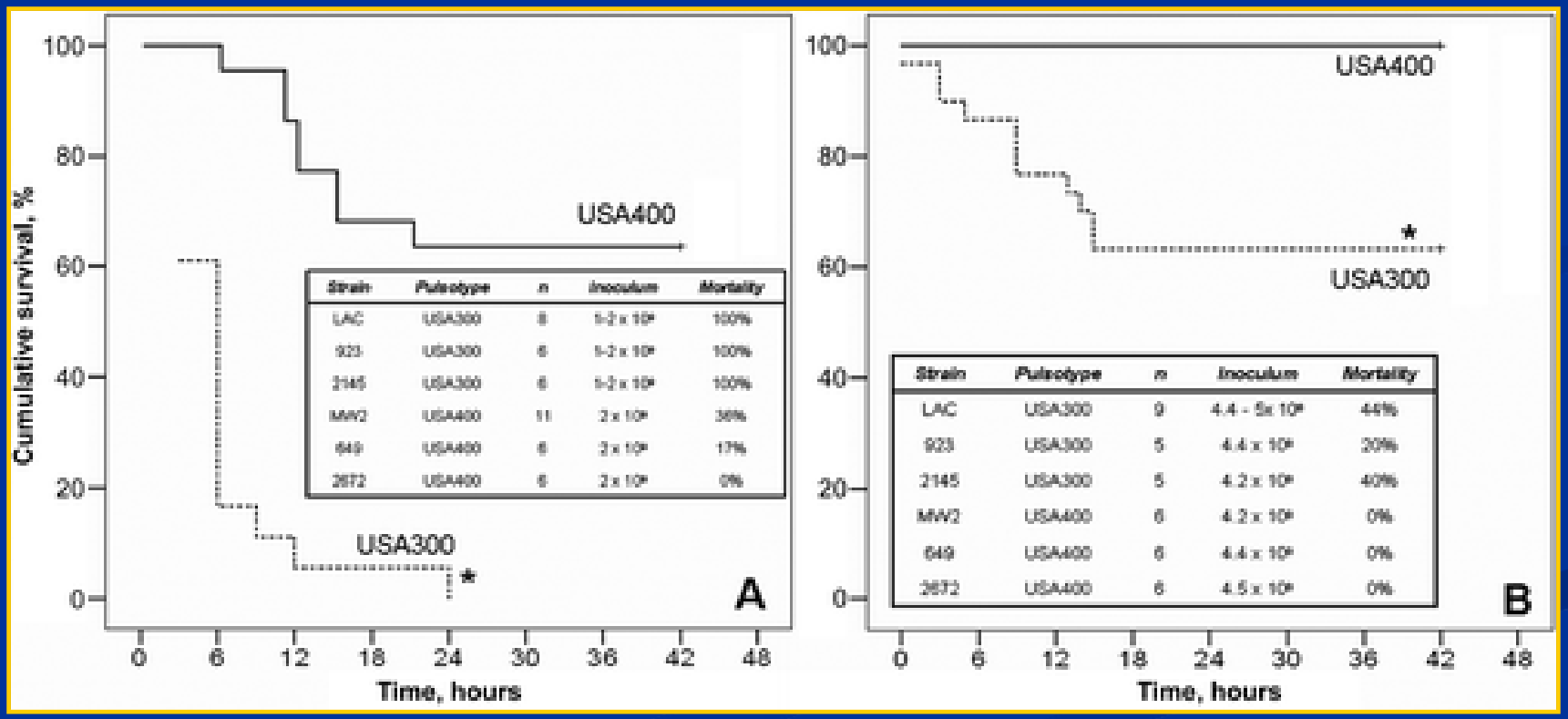


USA 300 – 31%
PVL – 42%

USA 300 More Virulent than USA 400 Rat Pneumonia Model

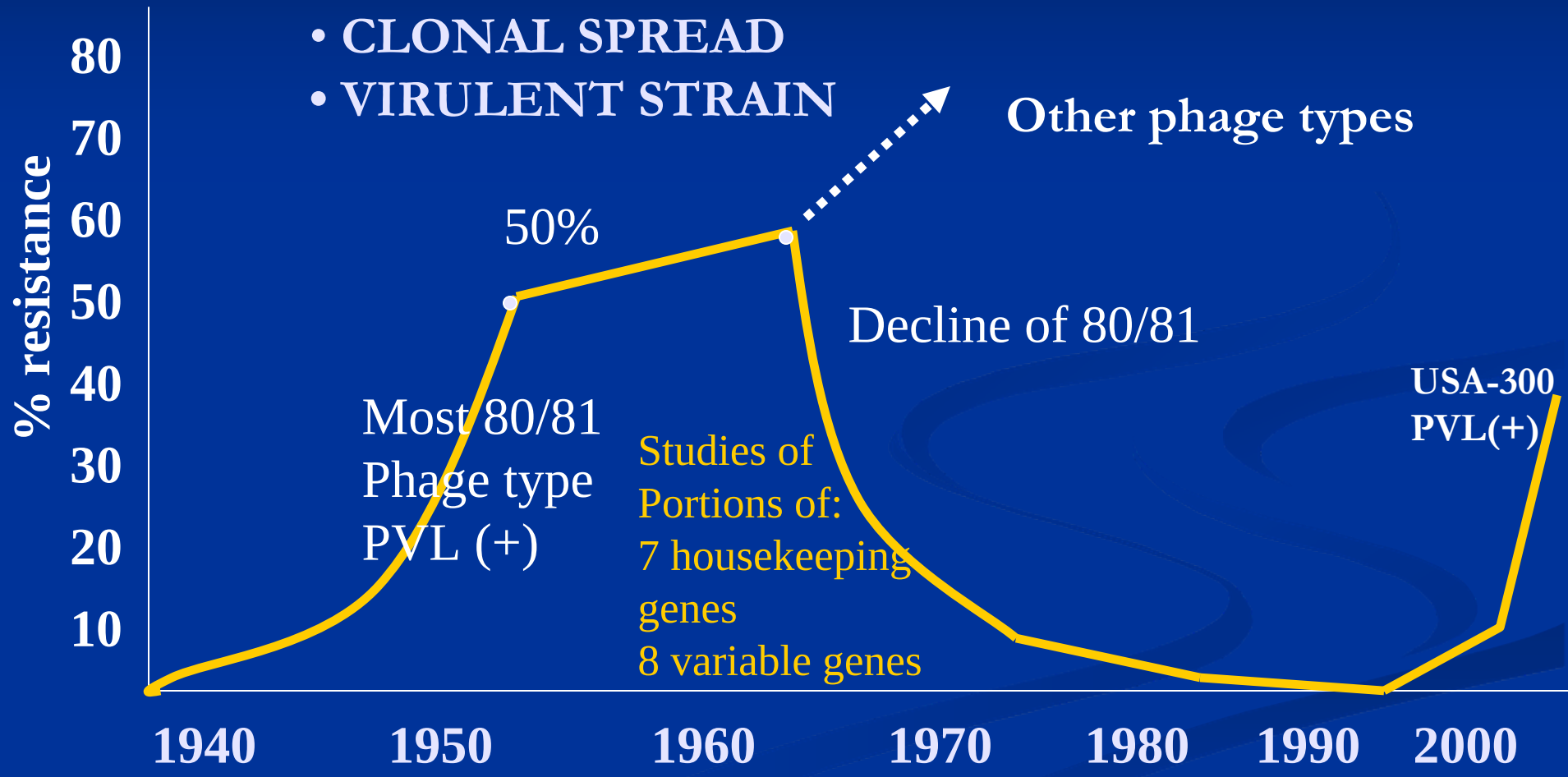
Comparison of USA300 and USA400 lethality

***P<.01, Fisher's exact test.**



Montgomery et al *JID* 2008; 198:561-70

Descendants of 80/81 Re-Emerging as CA-MRSA: Lessons after 70 years 1940-2010



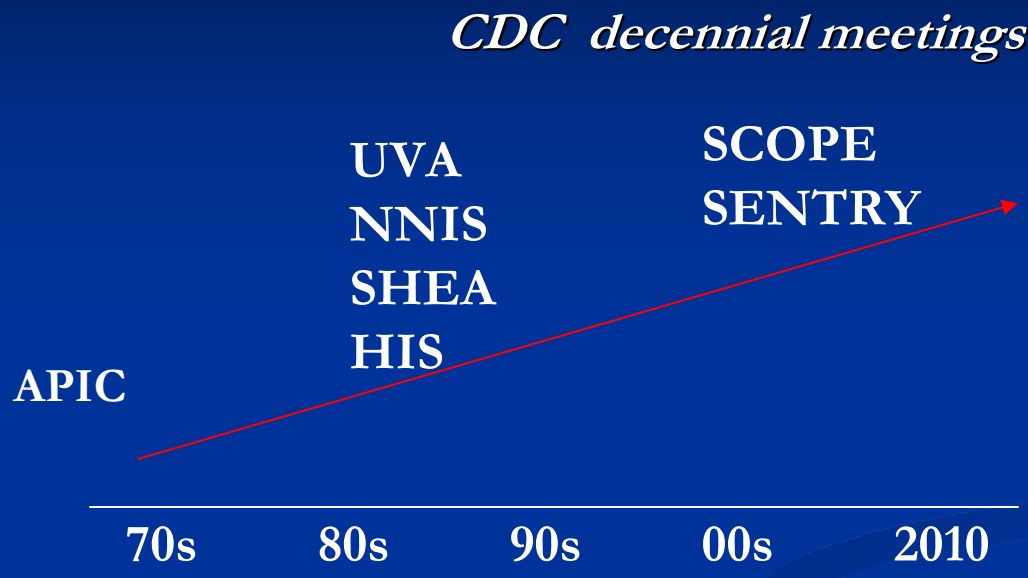
Robinson et al. *Lancet* 2005; 365:1256-8

So Far…

- *S. aureus* infections and modern hospitals have been constant companions
- Resistance patterns arise primarily from horizontal gene transfer
- Evolution of *S. aureus* is clonal

  Some strains (meth ® USA 300 *nee* PEN ® 80/81) are more virulent, spread more rapidly than others, and dominate

The Role of Modern Infection Control



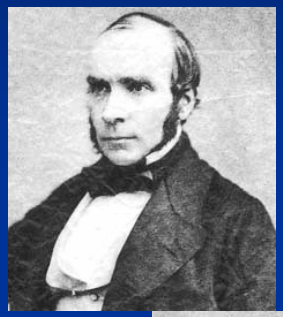
- Defining the unacceptable (*descriptive*)
- Modelling the possible (*analytical*)
- Testing the interventions (*intervention*)
- Executing good practice (*policy*)

Milestones in Surgery

Control bleeding
- Cauterize
- Sutures

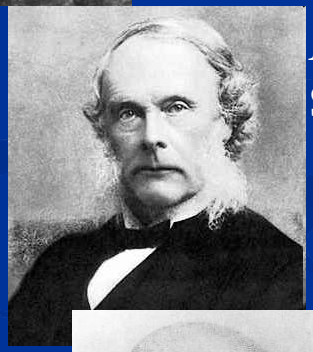
Ambrose Pare
(1510-1590)

John Snow
(1813-1858)



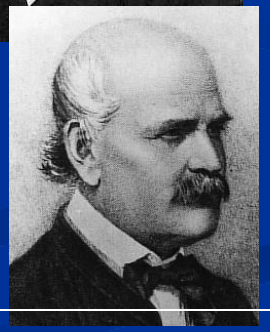
- Abandon Blood-letting
- Transfusion
- Anesthesia

Joseph Lister
(1827-1912)



Antisepsis
Sterile surgery

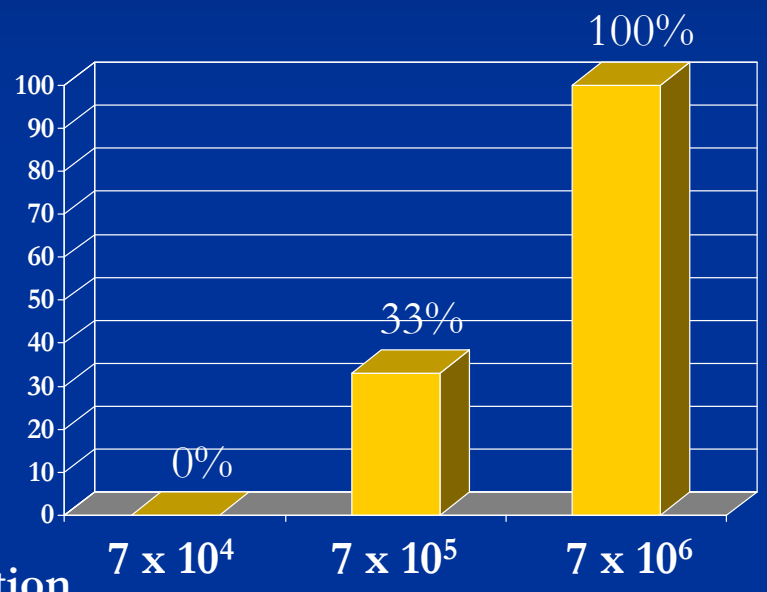
Ignaz Semmelweis
(1818-1865)



- Handwashing
- Antisepsis

16th or earlier century | 17th | 18th | 19th | 20th

Silk Sutures Reduce Infecting Dose of *S. aureus* by 4 logs



Similar Data:
- SubCU Injection
- Skin incision

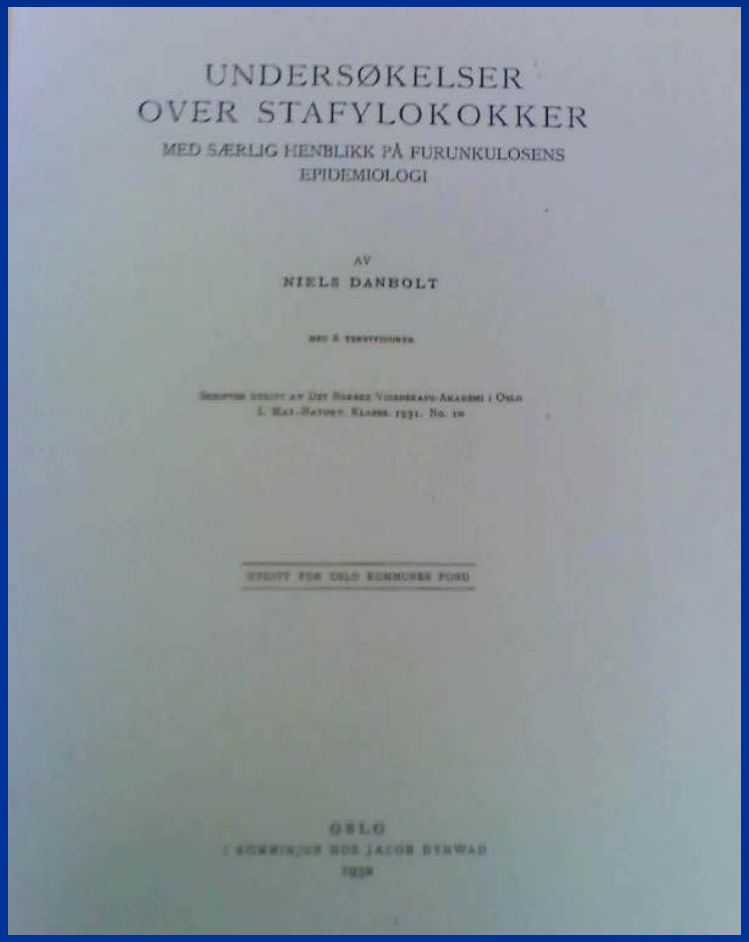
EFFECT OF SUTURES

Tied suture 3 x 10^4 organisms:
2/2 "very large stitch abscess"

Suture 3 x 10^2 organisms:
"small stitch abscess"

Elek and Conan *Brit J Exp Path* 1957; 38: 573-86

Niels Danbolt
Norwegian dermatologist
(1900-1984)



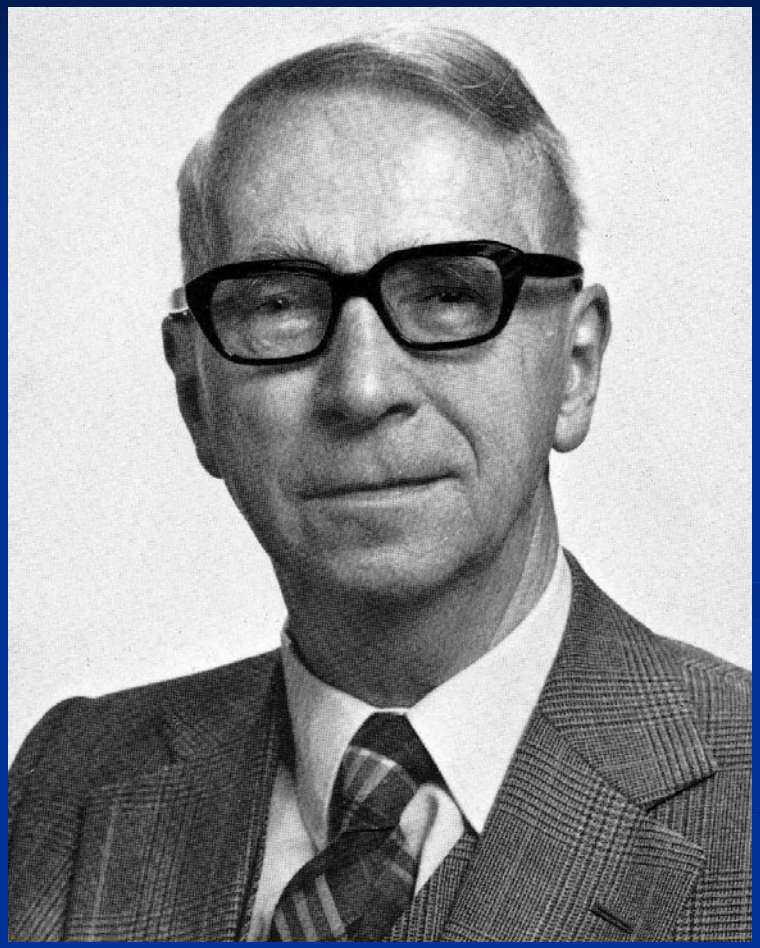
UNDERSØKELSER
OVER STAFYLOKOKKER

MED SÆRLIG HENBLIKK PÅ FURUNKULOSENS EPIDEMIOLOGI

AV
NIELS DANBOLT

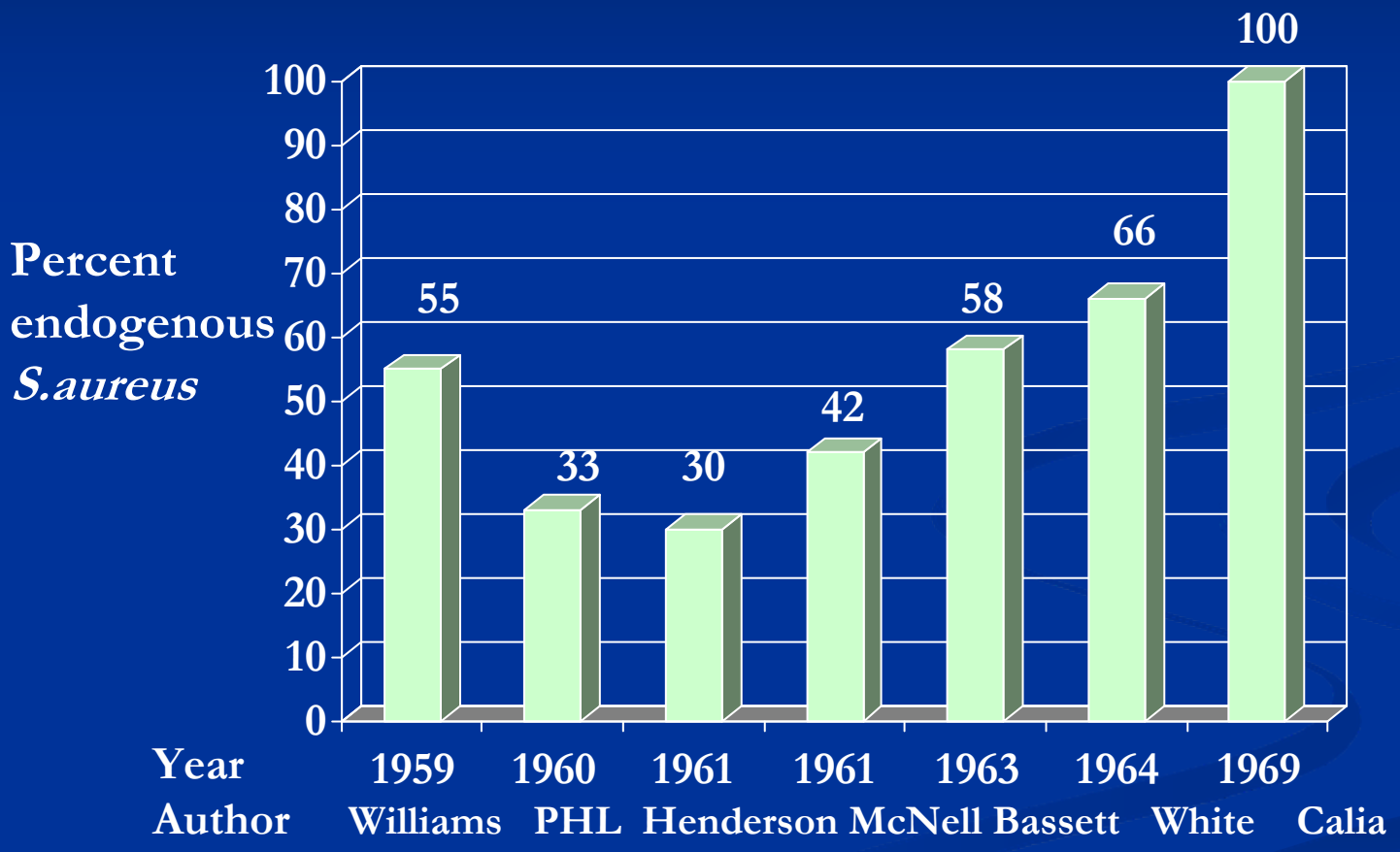
OSLO

- Typing - Coagulase
  - Biochemical Reaction
  - Necrotizing toxin (skin)
  - Clumping with specific rabbit antibody
- Furunculosis (n=50): 77% nasal carriage same strain
- Recurrent furunculosis (n=24): 22 had same strain in nose
- Healthy controls – 40% carry Staphylococci



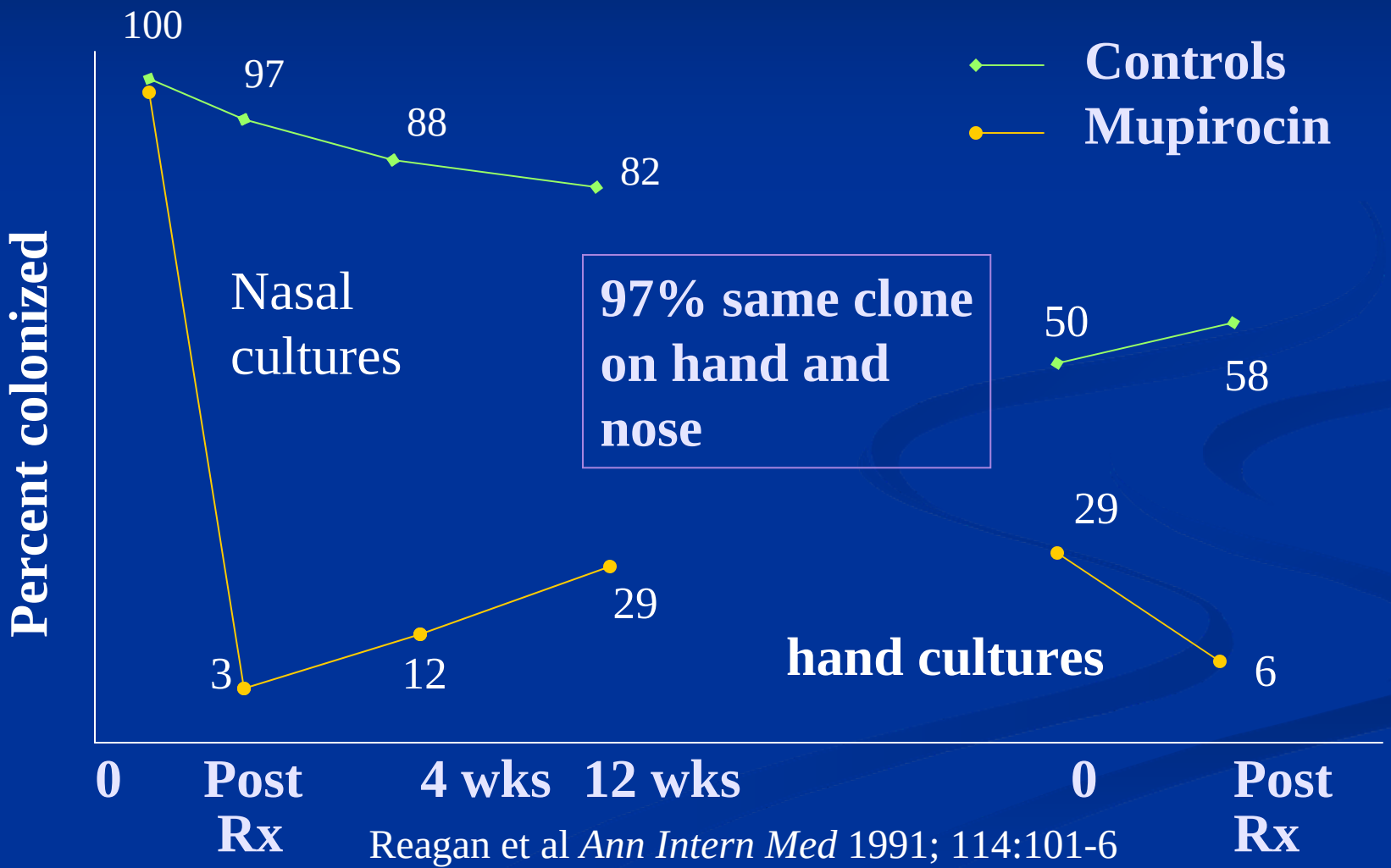
Courtesy of Niels Chr. Danbolt, PhD, University of Oslo

Median of 55% of *S.aureus* Surgical Site Infections are Endogenous



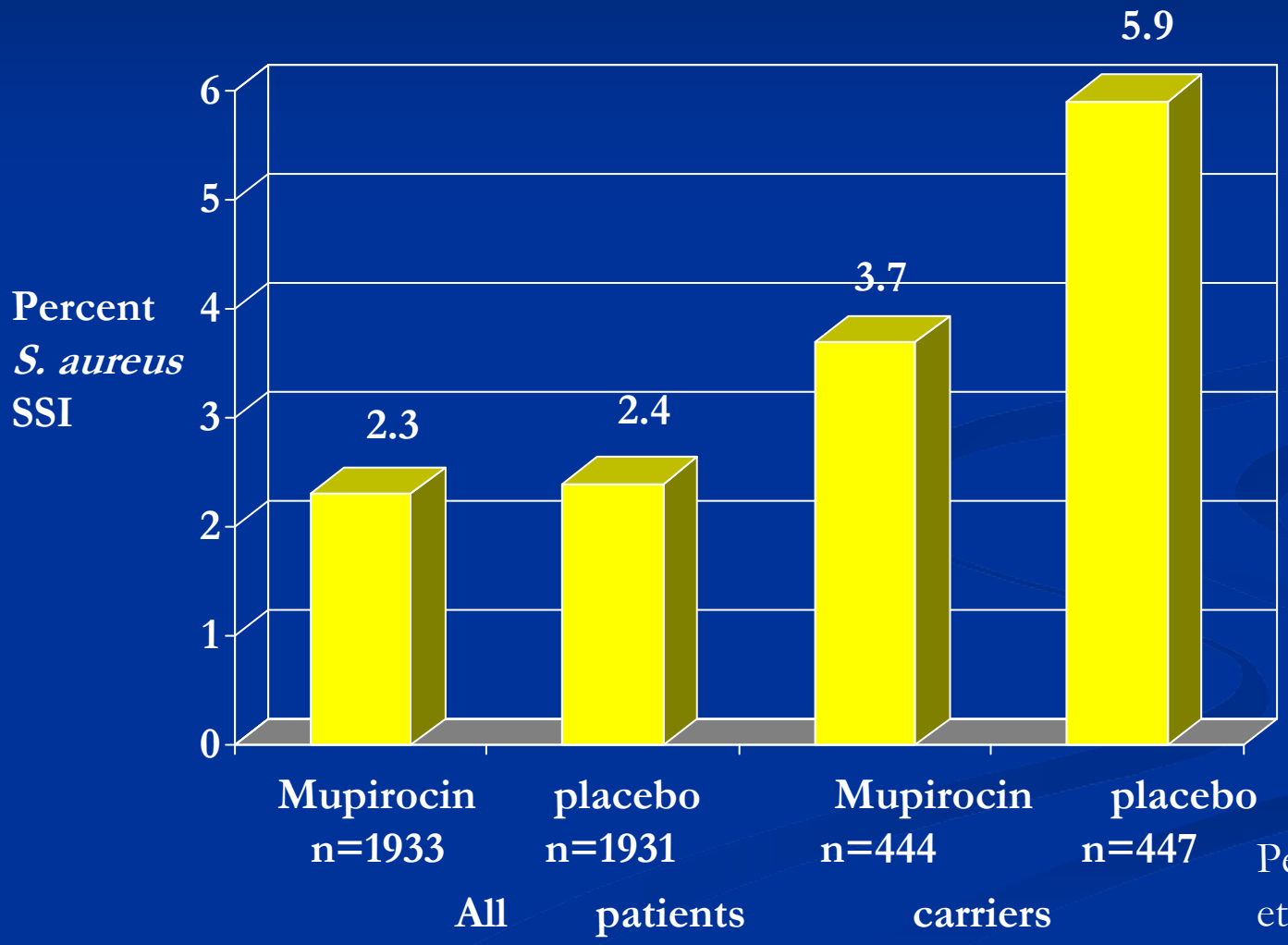
Wenzel and Perl *J Hosp infect* 1995; 31:13-24

Elimination of Coincident *S. aureus* Nasal and Hand Carriage with Mupirocin



Reagan et al *Ann Intern Med* 1991; 114:101-6

Intranasal Mupirocin to Prevent *S.aureus* Post-Surgical Infection



Perl, Cullen, Wenzel et al *NEJM* 2002; 346:1871-7

Subset of *S.epidermidis* Secrete Esp Inhibiting *S.aureus* Nasal Colonization

45% of 960 volunteers *S. epi i*nhibit biofilm of *S. aureus*

If colonized with inhibitory *S. epi*

OR=0.30 for *S. aureus* colonization

Esp, serine protease, plus peptide component of innate immune system (hβD2)* kill biofilm

Esp intoduced into nares, eliminates *S. aureus* colonization

* Human β-defensin 2

Iwase et al *Nature* 20 May 2010
Doi:10.1038/nature09074

Host Genetics May Determine Persistent *S. Aureus* Carriage

Persistant Carriage is Major Risk for Auto Infection

Lancet 2004; 364:703-5; *NEJM* 2001; 344: 11-16

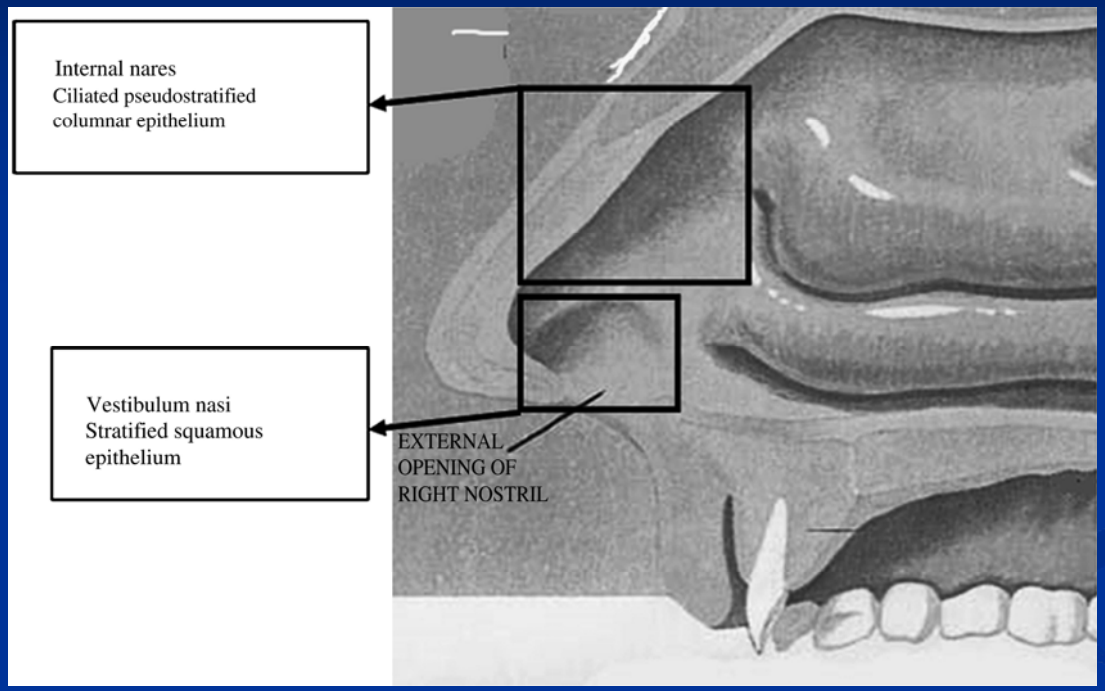
And is influenced by genetic variation in host inflammatory genes

J Infect Dis 2008; 197:1244-53

A significant association with persistent carriage (2006 and 2008) and sets of single nucleotide polymorphisms to CRP genes and IL-4 genes.

J Infect Dis 2010: 202: 924-34

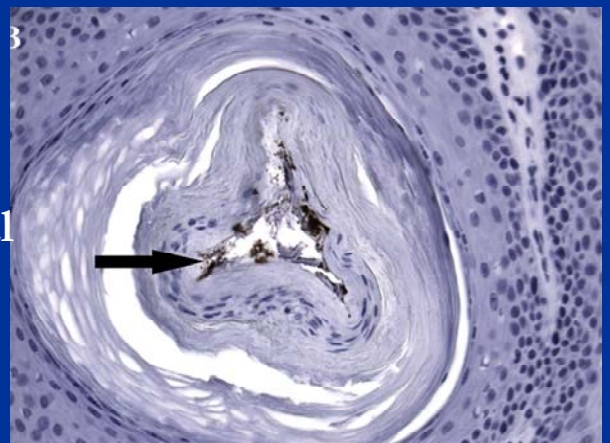
Hair Follicles as a Niche for *S.aureus* in the Nose



37 cadaver noses

S. aureus culture 9/37

SpA-specific antibodies in 8/9



ten Broeke-Smits et al
J Hosp Infect 2010;
76:211-4

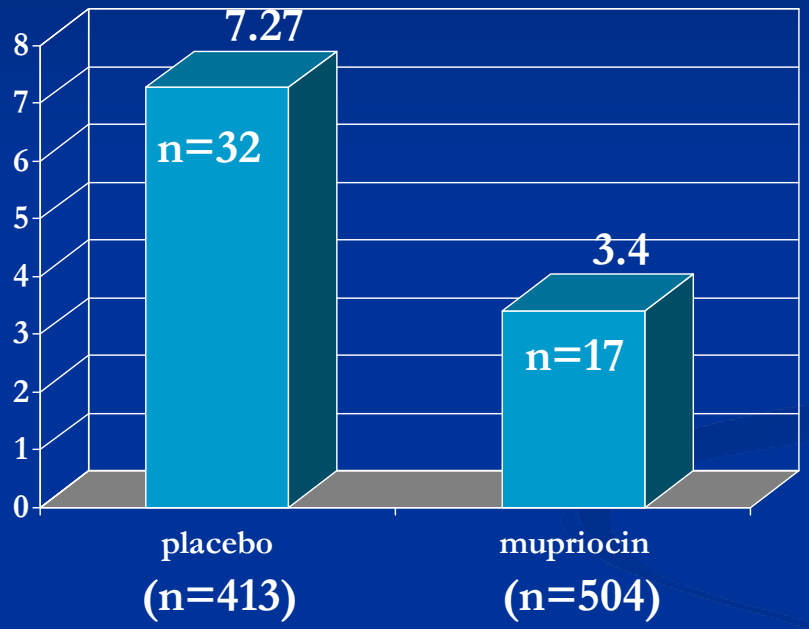
8/8 only in Vestibulum nasi

6 – only outer portions of hair follicle

2-deeper parts of hair follicle

Preventing Surgical-Site Infections in Nasal Carriers of *Staphylococcus aureus*

- Screening
- Mupirocin
- Chlorhexidine baths

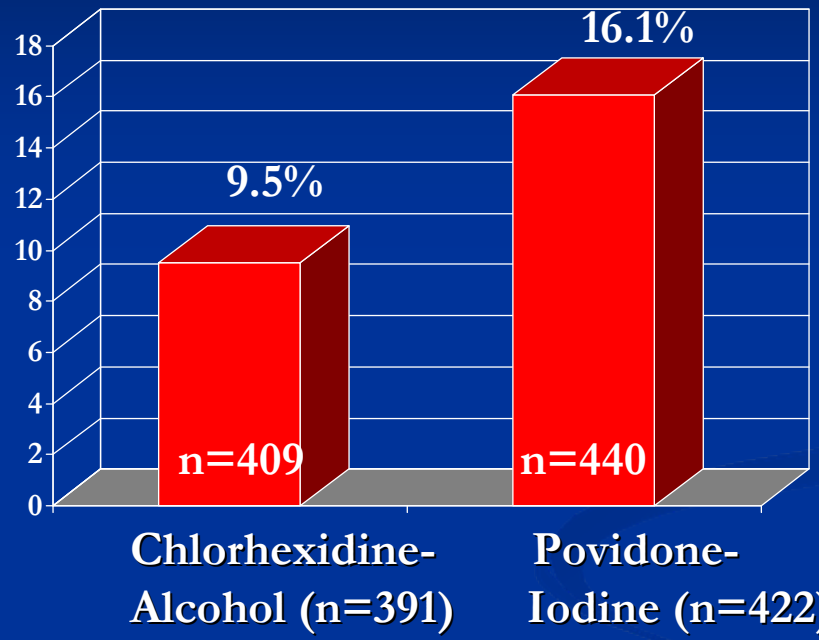


- ~60% reduction of S aureus infections
- 79% reduction in deep SSI
- 55% reduction in superficial SSIs

Bode LGM, et al. *N Engl J Med* 2010; 362: 9-17

Chlorhexidine-Alcohol vs Povidone-Iodine for Surgical-Site Antisepsis

SSI within 30 days



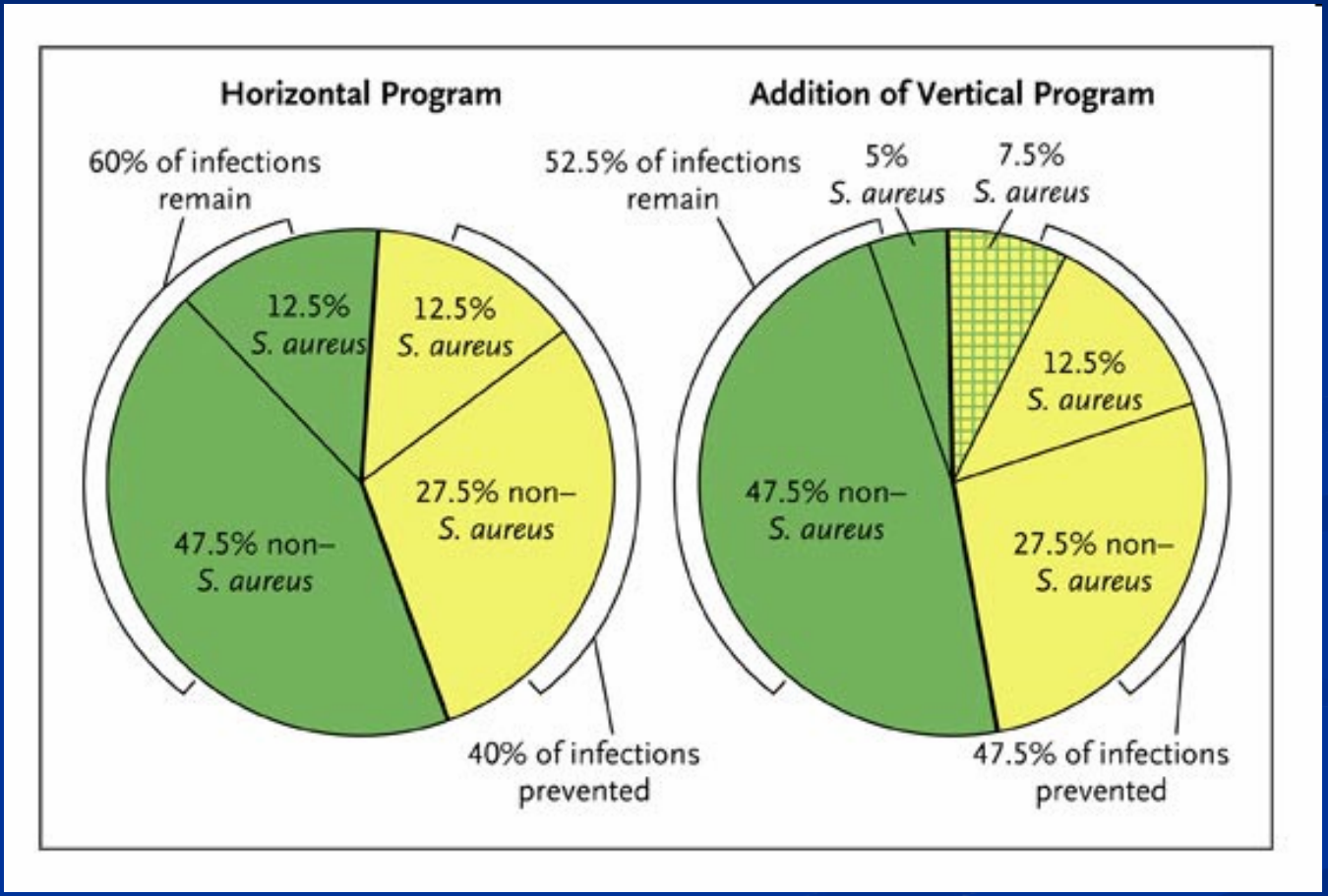
RR=.59

- Clean-contaminated surgery, randomly assigned to preoperative skin prep with either chlorhexidine-alcohol or povidone-iodine paint and scrub
- 6 hospitals
- 50% of S.aureus SSI prevented without a screening program

RR-Risk Ratio

Darouiche R, et. al *N Engl J Med* 2010; 362:18-26

Estimates of *S aureus* Infections Using Two Different Programs



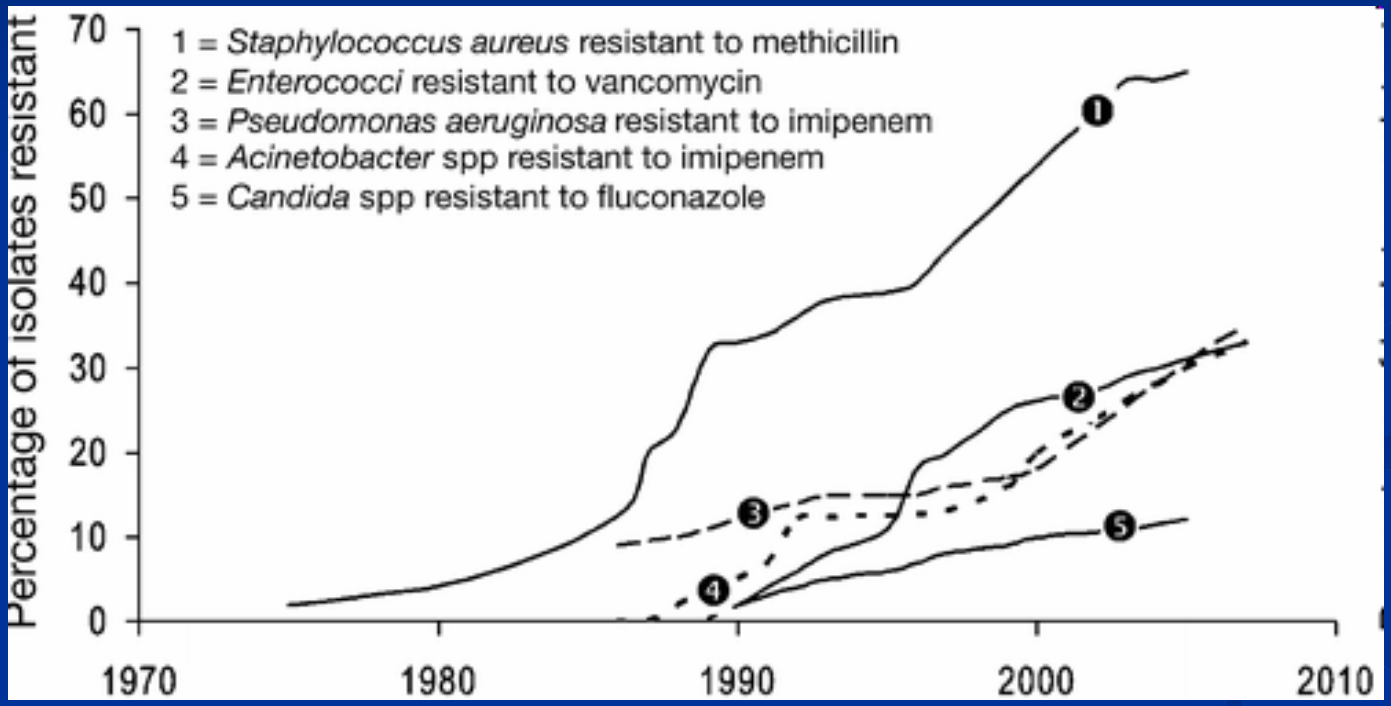
A horizontal program reduces all infections at a specific anatomic site, whereas a Vertical program targets a single organism at that site.

Wenzel R. *N Engl J Med.* 2010; 362:75-77

So Far…

- 40% of ALL SSIs can be eliminated with a change in surgical scrub from Iodophor to Chlorhexidine-Alcohol; 60% of *S. aureus* SSIs can be eliminated with Chlorhexidine baths and mupirocin Rx of carriers
- Combining both approaches might yield a 50% absolute reduction of all SSIs.

Increasing Antibiotic Resistance Strains 1970-2010



Wenzel et al *ICHE* 2008; 29:1012-8

Health care associated MRSA 2005-2008: 28% decline in US
Kallen et al *JAMA* 2010; 304:641-8

The Shortcomings of Nasal Screening for *S. aureus*/MRSA

Throat carriage only in *S.aureus*: 25%

MRSA throat carriage only: 13-15%

***Arch Internal Medicine* 2009; 169:172-8**

***Journal of Clinical Microbiology* 2008; 46:835**

***Journal of Clinical Microbiology* 227; 45:385**

CA-MRSA in Nares Only in 41%

***ICH* 2007; 28:966-9**

Caveat: Does extranasal carriage have same risk as nasal carriage?

Decline in Invasive MRSA Infections

CDC's population-based surveillance

2005-08: Decline 9.4%/yr

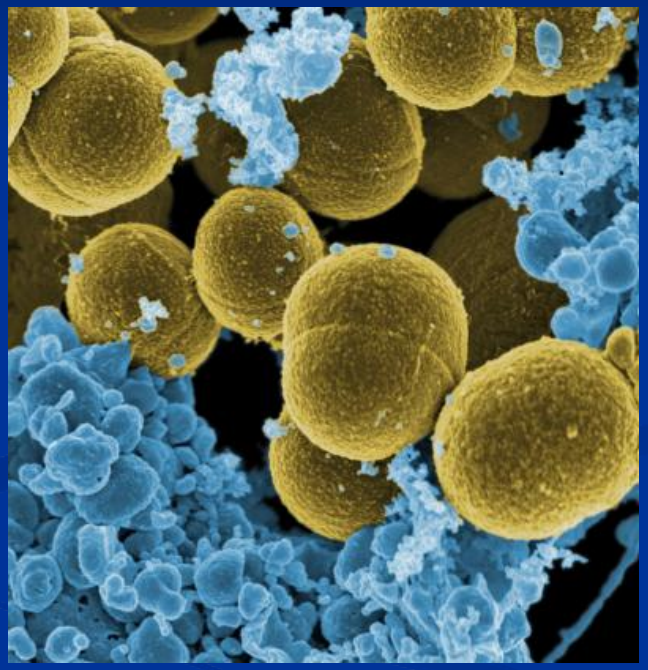
- most prominent for BSIs
- 28% decline over 4 years

National decline of MRSA BSI

- 2003-08: 57%

Declines began prior to MRSA-specific interventions

Possible causes: horizontal programs vs unexplained biological trends

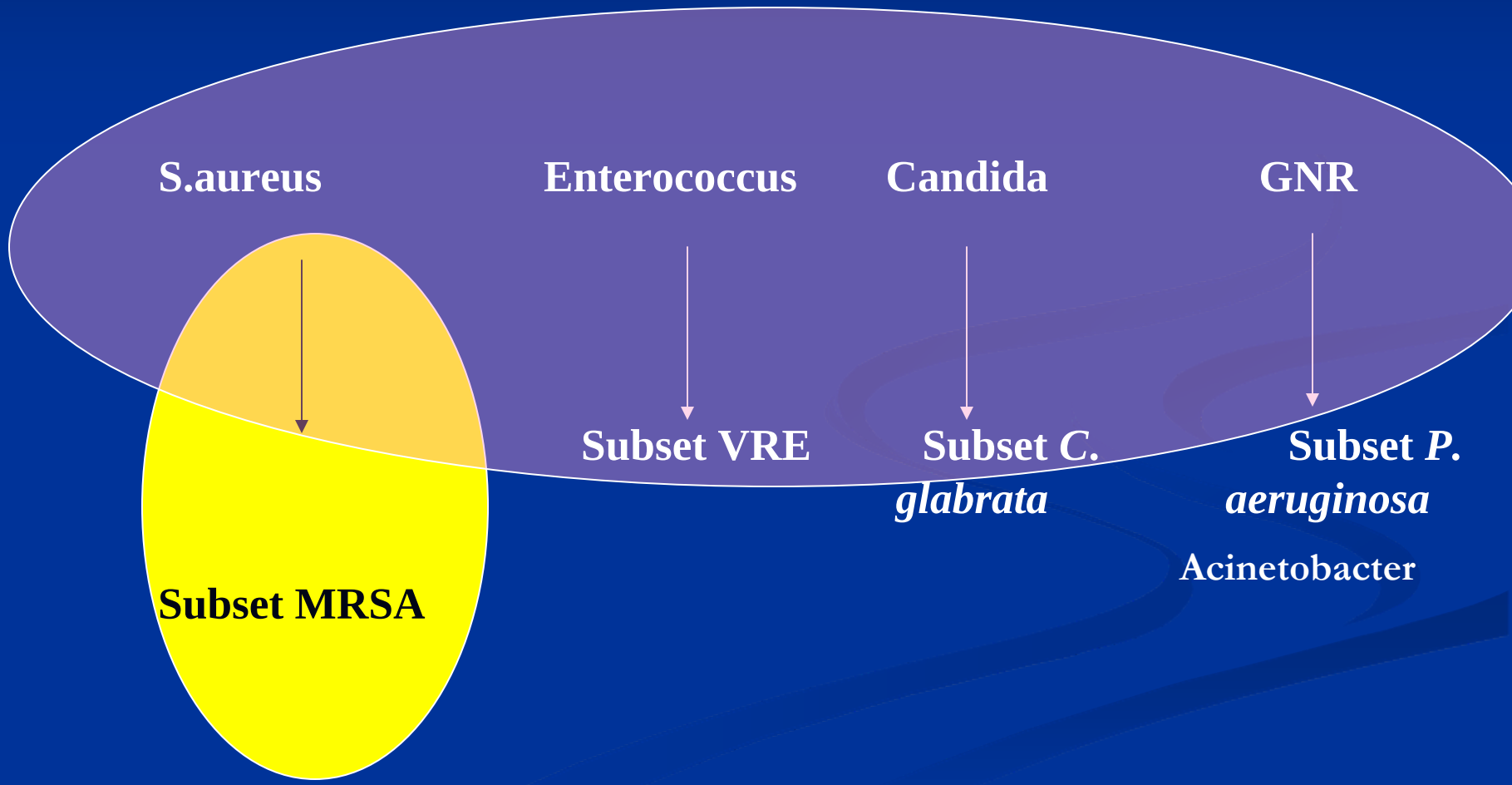


JAMA **2010; 304:641-8**

JAC **2009; 64 (supp 1):111-7**

JAMA **2010; 304:687-9**

Controlling Healthcare Associated BSI: Vertical vs Horizontal Approach



Daily 4% Chlorhexidine Baths Decreased ICU-related MDR *A. baumannii* Colonization and Bloodstream Infections by 85%

Quasi-experimental design

Before 2/01 – 2/02) – after (3/02 – 12/03) comparison

Attack rate of *A. baumannii*

BSI – decreased

4.6% => 0.6% (OR=7.6, p<.001)

Incidence density of *A. baumannii*

BSI – DECREASED

7.8 to 1.25/1000 pt-days (85% reduction)

Borer et al. *J Hosp. Infect* 2007; 67:149-55

Could Daily Bathing with Chlorhexidine Reduce MRSA and VRE Acquisition and Infections?

In quasi-experimental study

6 mo reg soap => 6 mo chlorhexidine

- MRSA acquisition decreased 32%
- VRE acquisition decreased 50%
- **VRE BSI decreased 73%**

***Crit Care Med* 2009; 37:1858-65**

Medical College of Virginia Hospital Evidence-Based Interventions (without active surveillance for MRSA)

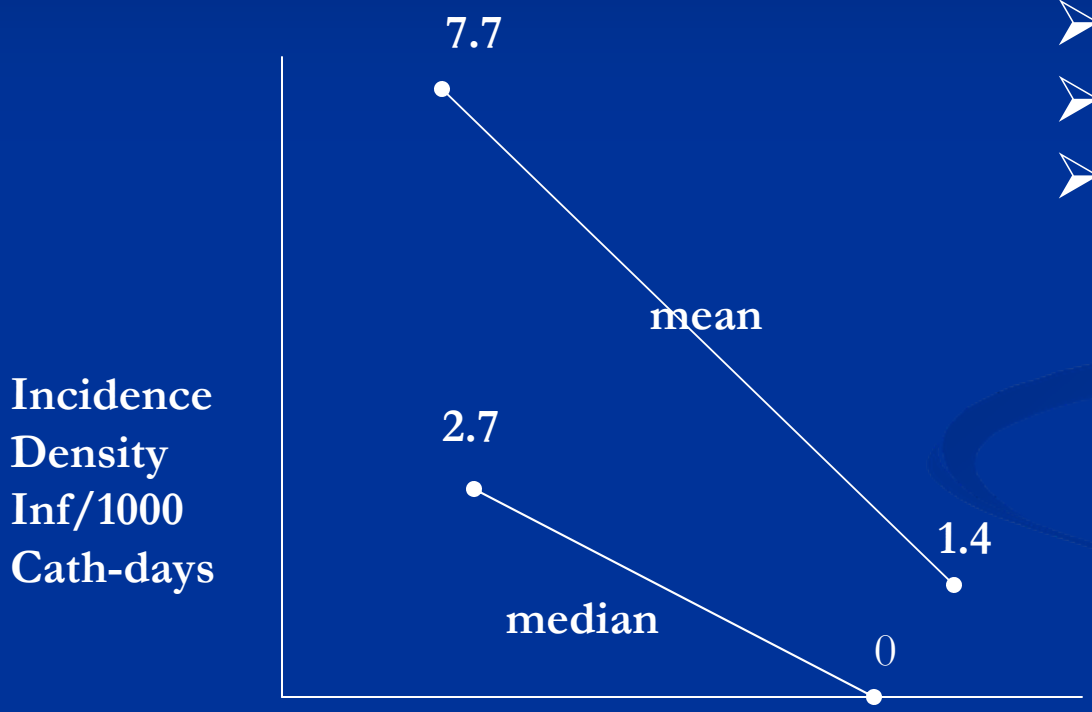
Neuroscience, Medical, Surgical ICUs

Device-related BSI, urine infections and VAPs fell > 40% in each unit and MRSA infects fell >48% in each unit

1 July 2010: 914 days in MRICU wince VAP case

Edmond et al *Am J Infect Control* 2008 ; 36:461-3

66% Reduction in all Catheter-related Bloodstream Infections



- 103 ICUs
- Check list approach
- Empowered team

NEJM 2006; 355:2725-32

Bundles to Remove all Central Cath-Related BSIs

Insertion

- Aseptic Technique
- Maximal Barrier Precautions
- Chlorinex/Alcohol Prep
- Avoid Femoral Site
- Use CVC Check List
  - Operator Name
  - Completed CVC Education

BMJ Qual Saf 2011; 20: 174-80

Maintenance/Removal

- Remove ASAP
- Hand Hygiene Before
- Clean Part With Alcohol
- Avoid 3-Way MPS
- Needless Adaptors For Ports
- Inspect/Clean Site Daily
- Dedicated Lumen For TPN

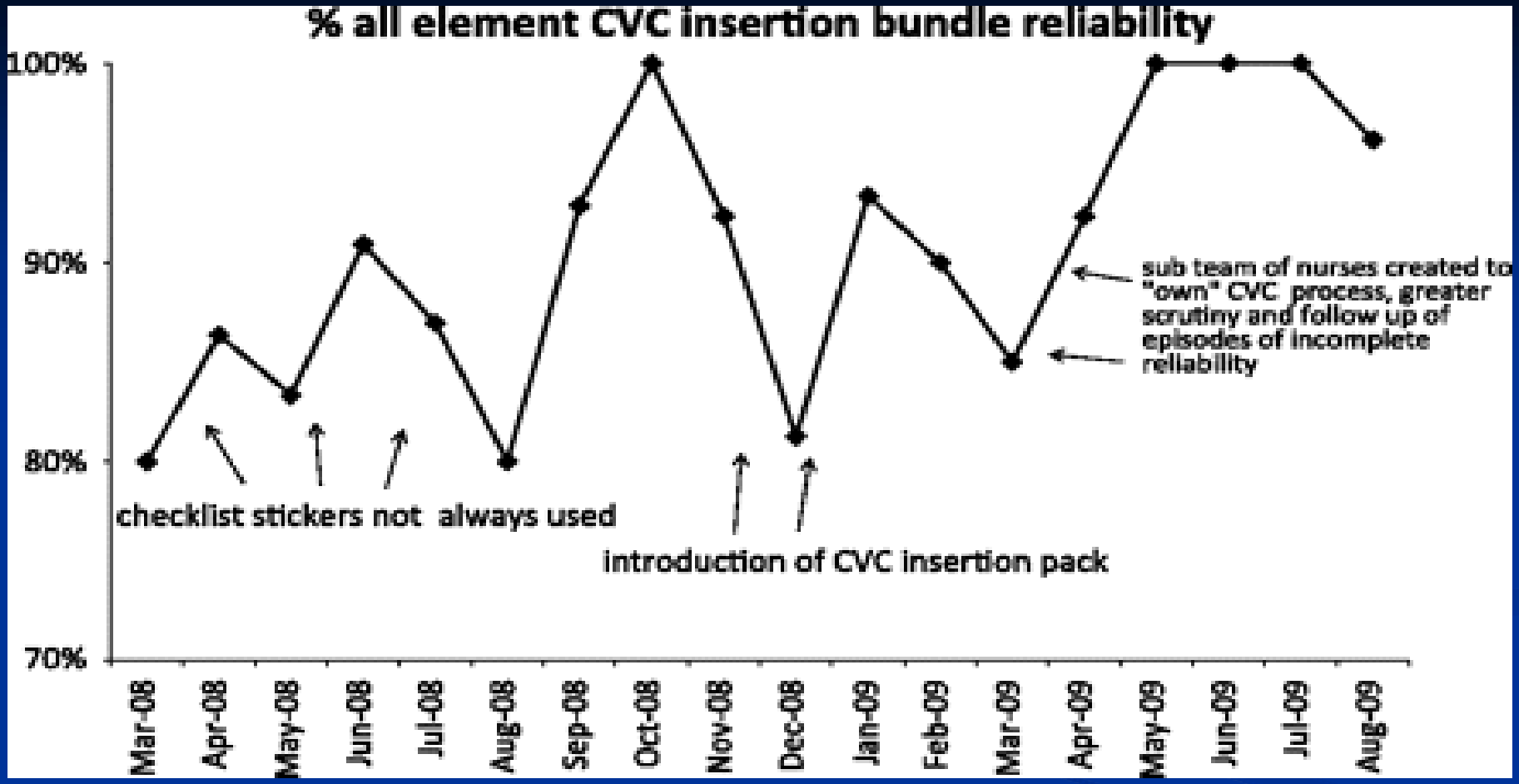


Figure 1

All or none insertion bundle reliability over time annotated to show identification and resolution of causes of incomplete reliability. Detail is given in the online appendix 6. Reliability increased between March 2008 and August 2009.

BMJ Qual Saf 2011;20:174-180. doi:10.1136/bmjqs.2009.037200

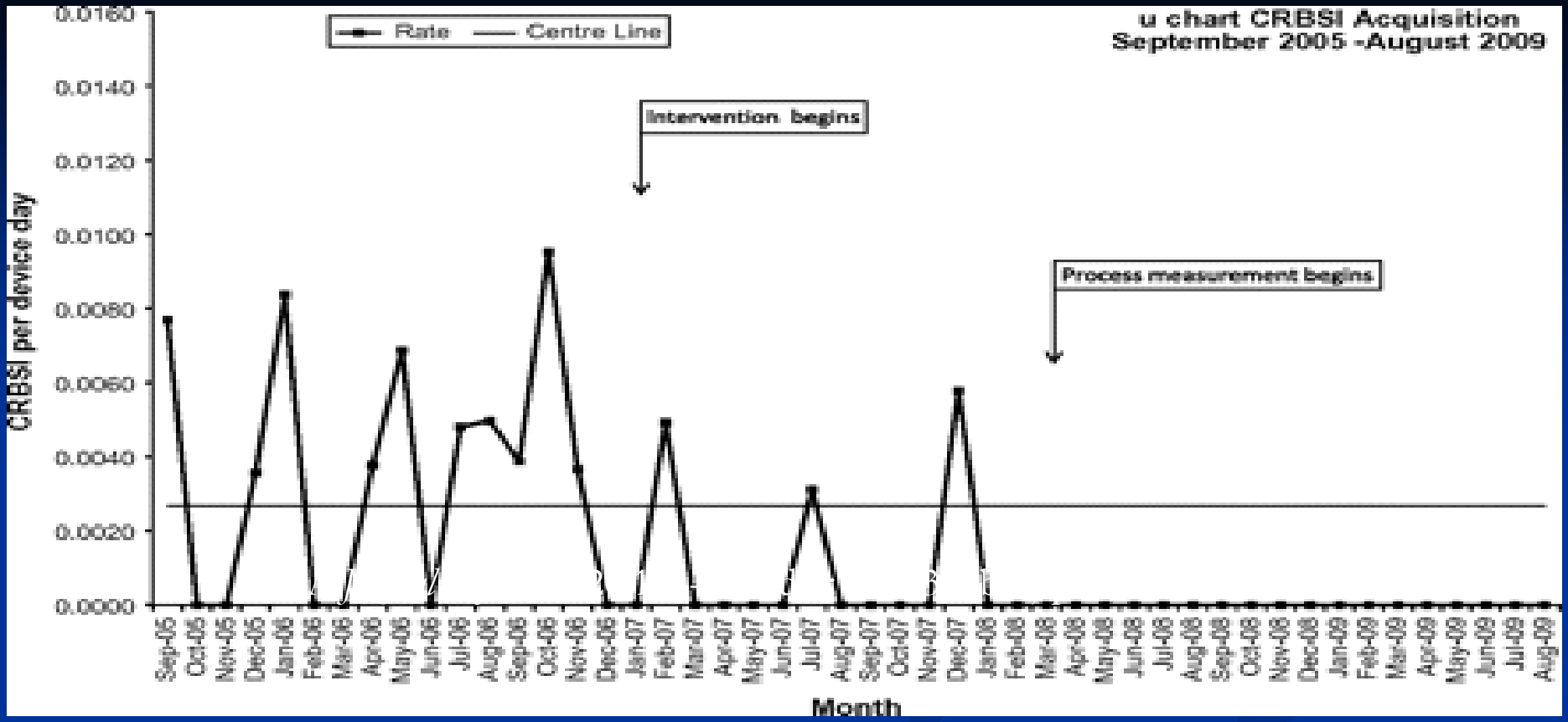


Figure 2

U chart. Monthly central-venous-catheter-related bloodstream infection (CRBSI) acquisition as rate per device day (number of infections divided by the device days/month). The plot demonstrates the common cause variation before the interventions start. Special cause variation (downwards shift) is evidenced by a run of >6 points below the centre line from February 2008.

BMJ Qual Saf 2011;20:174-180. doi:10.1136/bmjqs.2009.037200

Reducing Ventilator-Associated Pneumonia by 71% - Cohort Study

112 ICUs and 32278 ICU – Months. Bundle:

- Semi-recumbent position
- Adjustment of sedation to allow patient to follow commands
- Daily assessment of readiness to extubate
- Stress Ulcers Prophylaxis
- Prophylaxis to decrease DVTs

Caveats: No controls; no uniform surveillance definition

ICHE 2011; 32:305-14

Reducing Ventilator Associated Pneumonia by 71% - Cohort Study

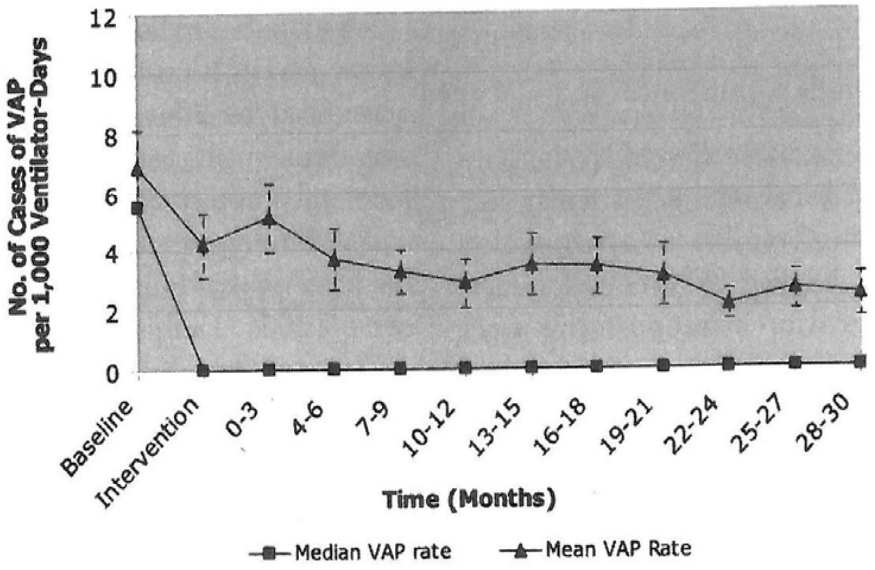


FIGURE 1. Quarterly ventilator-associated pneumonia (VAP) rate through 28–30 months after implementation. Shown are the median and mean (95% confidence intervals) VAP rates over time. $P < .001$ (2-sample Wilcoxon rank-sum test) for comparison of the preimplementation baseline period with 16–18-month and 28–30-month postimplementation periods.

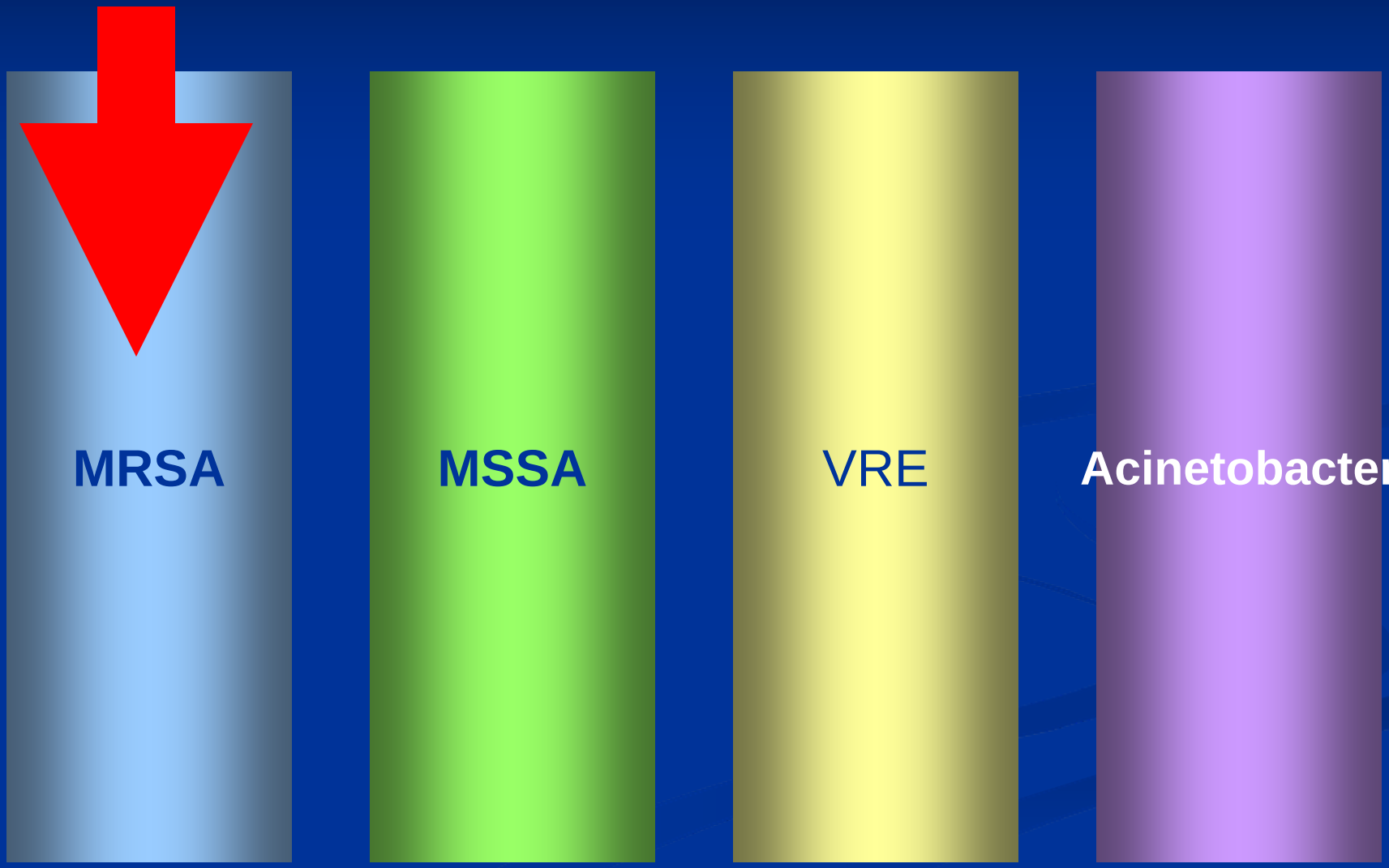
Why Do Horizontal Programs Work? They Are Population-based: BSI example

Comparison of infection control approaches assuming 10,000 admissions and 500-1000 infections (5-10% rate)

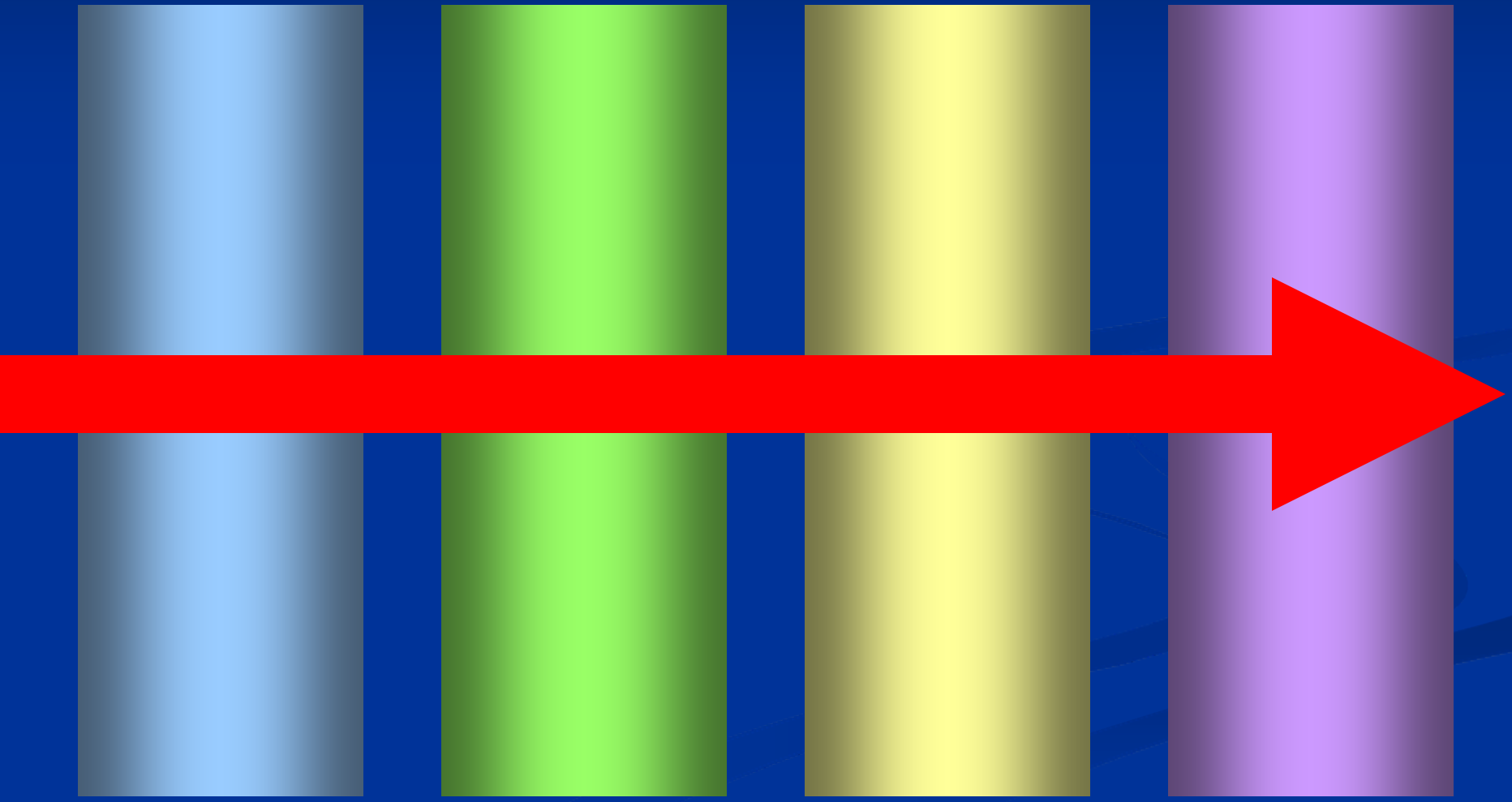
	Population based	MRSA-Subset
Bloodstream infections*	50-100	7-14†
Number of deaths estimated**	13-25	2-4
Attributable deaths***	7-13	1-2
Lives saved if attributable deaths Prevented by 50%	4-7	1-1
National estimates of lives saved (assume 35 million admissions – 3500 fold greater than 10,000)	14,000-24,500	3,500

Wenzel et al. *ICHE* 2008; 29:1012-18

Controlling Pathogens in the Hospital:
Vertical vs. Horizontal Approach



Controlling Pathogens in the Hospital:
Vertical vs. Horizontal Approach



Infection Control in 2011

Current data support the argument that we have the ability to reduce all nosocomial infections by 50%, including MRSA, VRE,

and MDR Acinetobacter

See Also:

Infect Control Hosp Epidemiol 2011; 32:101-14

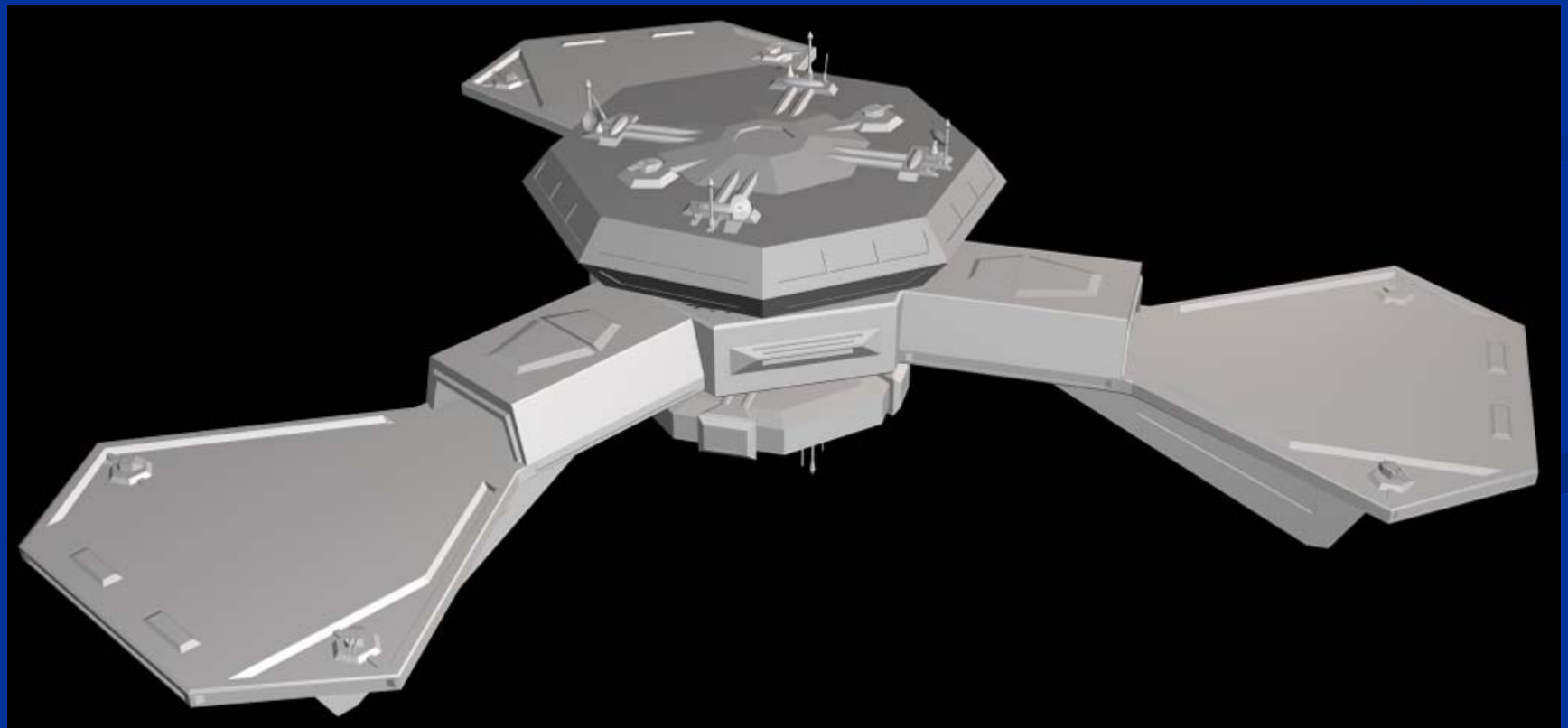
Caveat: Will we begin to see Chlorhexidine resistant strains emerge?

From 2011…

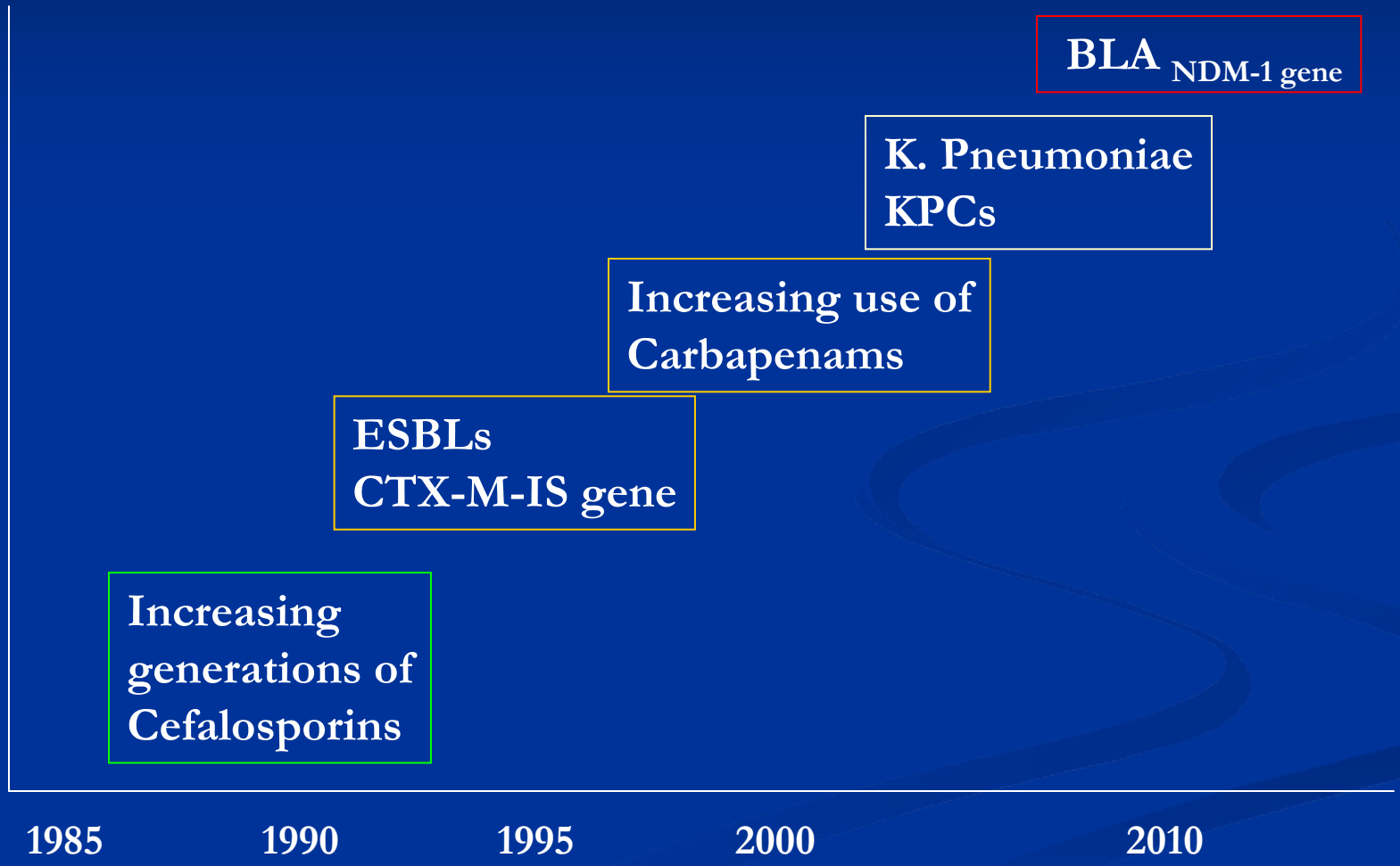
How do we prevent the existing infections by *another 50% in the next 3-4 years*… achieving a 75% total reduction by 2014-2015?

Key Infection Control Safety Question

On a platform of an effective infection control program (~ 50% reduction in <u>all</u> infections every 3-4 years), what is the incremental value of an adjunctive vertical program (MRSA screening)?

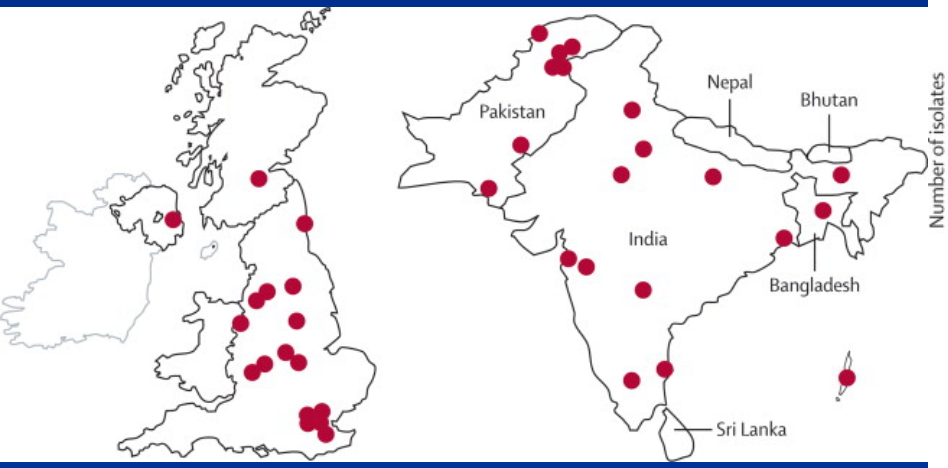


Emergence of New Delhi Metallo-β-lactamase

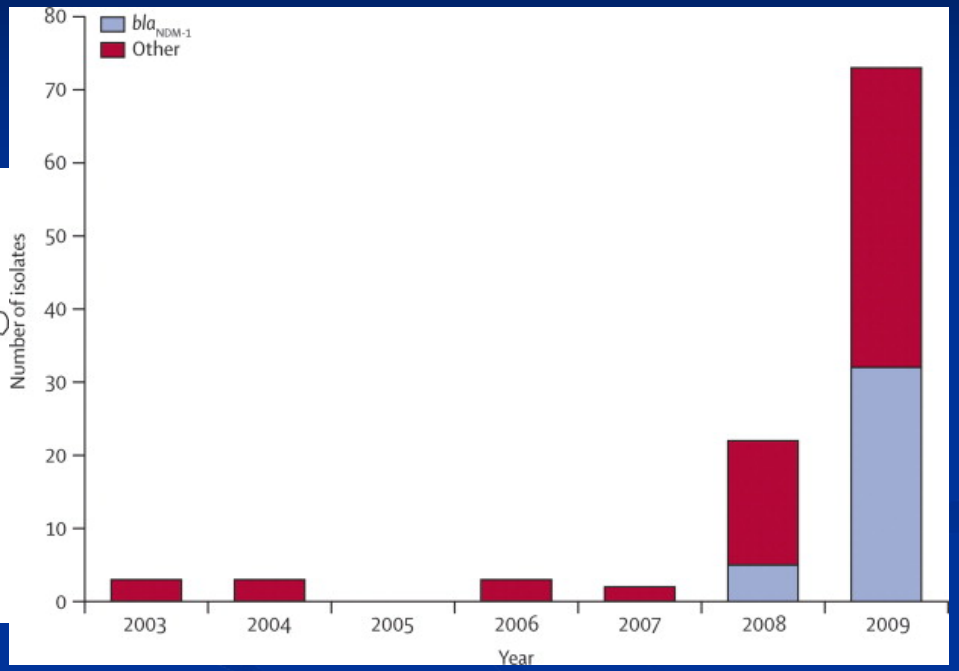


Lancet Inf Dis 2010; 10:597-602

NDM-1 in India, Pakistan, and UK



Distribution of NDM-1-producing Enterobacteriaceae strains in Bangladesh, India, Pakistan, and the UK



Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency's national reference laboratory from 2003 to 2009. The predominant gene is *bla*NDM-1, which was first identified in 2008. The other group includes diverse producers of KPC, OXA-48, IMP, and VIM enzymes.

Lancet Inf Dis 2010; 10:597-602

Final Questions

- Can we begin to think about infection control and antibiotic resistance as a global health problem?
- Can we construct global health policies and strategies that benefit the developing and developed world equally?